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Inorganic Arsenicals (Non-Wood Use) Position Document 1

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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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INORGANIC ARSENICALS: Position Document 1

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INORGANIC ARSENICALS (Arsenic Acid, Arsenic Pentoxide, Arsenic Trioxide, Sodium Arsenate, Ammonium Arsenite, Sodium Pyroarsenate, Lead Arsenate (Standard and Basic), Calcium Arsenate, Sodium Arsenite, and Copper Acetoarsenite): POSITION DOCUMENT 1

SUMMARY

Arsenic is an ubiquitous element that occurs naturally in soil, water, microorganisms, plants, animals, and humans. This document focuses on those pesticides containing inorganic arsenic (ammonium arsenite, arsenic acid, arsenic pentoxide, arsenic trioxide, calcium arsenate, copper acetoarsenite, lead arsenate, sodium arsenite, sodium arsenate, and sodium pyroarsenate). These pesticides are in the form of either arsenite or arsenate, both of which are found in nature.

Inorganic arsenicals were among the first chemical insecticides used, and they are still being used today as insecticides, herbicides, wood preservatives, and as a maturing agent for grapefruit. Tolerance levels for residues of inorganic arsenic pesticides have been set by EPA for various foods such as fruit, vegetables, and meats. Arsenic also occurs in food and feed as a natural constitutent.

Absorption of inorganic arsenic (from natural and pesticide sources) by plants from soil, water, and air is influenced by several factors. Aquatic animals ingest or absorb arsenic directly from the surrounding water; terrestrial animals are exposed primarily by ingestion of contaminated feed. Exposure to humans, primarily from pesticides and smelters, is by ingestion, inhalation, and absorption through the skin. In mammals, arsenite and arsenate are differentially absorbed through various body tissues (i.e., skin, lungs, digestive tract).

Arsenic is distributed in plant tissues primarily in the roots and vegetative tissues; fruits usually have the lowest levels of arsenic. Arsenic distribution in animals is influenced by several factors such as the form of arsenic, species of animal, and route of exposure (oral, dermal, inhalation). In mammals, including humans, inorganic arsenic is distributed primarily in the liver, lungs, kidney, and spleen. There are also high levels of arsenic bound in hair and nail tissue. Since arsenic is a natural environmental contaminant, it is always present in human and animal tissues. The normal adult human body contains an estimated 15 to 20 mg of arsenic.

The biochemical mechanisms of toxic action for arsenate and arsenite differ: arsenate blocks the formation of high energy compounds needed for cellular metabolism, and arsenite binds to proteins and inhibits the activity of several important enzymes. Arsenic does not normally build up beyond trace levels in mammalian tissues because a dynamic equilibrium is apparently reached between normal intake and excretion. Arsenite and arsenate are excreted at different rates: arsenate is generally excreted quickly from the body by the kidney, while arsenite is slowly excreted as it is released from tissue proteins to which it is bound.

Inorganic arsenic can be converted from one form to another by the metabolic activity of plant and animal cells. This is called biotransformation. In humans the conversion of arsenite to arsenate is favored, but animal studies have shown that arsenate can also be converted to arsenite. Both forms can also be converted to organic arsenic compounds such as methylarsenate. In soil, sediments of rivers and lakes, and water, transformation of arsenic (primarily to volatile organic forms) is mediated by microorganisms under both aerobic (oxygen present) and anaerobic (no oxygen present) conditions.

Although there are several source of inorganic arsenic (i.e., natural weathering of arsenic-containing rock, smelters, volcanic debris, and pesticides), residues from pesticides are a major source of arsenic pollution of soil, water, and air, and are the most widely distributed in the environment. Adsorption (adhesion) of arsenic to soil particles is dependent on several factors, and the adsorbed arsenic is fixed in the soil and is slightly soluble. The soluble unfixed arsenic is subject to leaching. Arsenic is naturally removed from the soil by volatilization (from biotransformation), leaching, wind-born dust, run-off, and plant uptake. Residues in soil from pesticide use are concentrated in the surface layers, and leaching usually occurs at a rate approximately equal to the addition of more pesticide. However, in some cases (i.e., apple orchards in Washington state), the extensive use of inorganic arsenicals has exceeded the leaching rate and rendered the soil very toxic to plants.

The content of arsenic is higher in sea water than in fresh water, except for fresh water near natural deposits of arsenic, areas of volcanic activity, or near pollution sources such as pesticide run-off. There is an equilibrium between arsenite and arsenate in sea water. In the upper oxidizing layers of the ocean, arsenic is primarily in the arsenate form; in the lower areas where reduction occurs, it is most often in the arsenite form. Arsenic is removed from solution by volatilization (from biotransformation) and adsorption by sediments.

Arsenic in air results primarily from human activities (i.e., smelting metals, ginning cotton, applying pesticides) and to a lesser extent from volcanic and bacterial action. Arsenic moves in air adsorbed to particulate matter and returns to soil by direct fallout and precipitation.

Arsenic apparently does not biomagnify: inorganic arsenic residues from pesticide use are not transferred from lower to higher organisms in the food chain, and therefore a greater concentration of arsenic does not occur in higher organisms than is present in lower forms. However, arsenic does bioaccumulate: residues can build-up in certain species. Due to the higher concentration of arsenic in salt water, marine organisms (plant and animal) tend to accumulate arsenic to a greater extent than freshwater forms. Lower food chain forms (plankton) usually have the highest arsenic residues.

The oncogenic, mutagenic, and teratogenic effects of inorganic arsenical pesticides are described in studies presented in this document. These effects are due to the action of the arsenate or arsenite portion of the parent compound rather than the compound as a whole (i.e., lead arsenate, sodium arsenite).

Therefore, if any arsenite form of arsenic produces a given effect, it is assumed that all arsenites are capable of producing the effect. The same is assumed for arsenates. There is also interconversion of the two forms in the body (arsenate reduced to arsenite, arsenite oxidized to arsenate). In mammals, conversion of arsenite to arsenate in the body is well documented. There is also evidence that arsenate can convert to arsenite *in vivo*, but this is less well-documented.

Arsenic is unique as a suspect carcinogen because an animal testing system has not yet been found that produces a carcinogenic response in rodents. There are numerous human epidemiology studies, however, which describe oncogenic effects from long-term exposure to arsenite and arsenate. These include the chronic use of potassium arsenite (Fowler's solution) for medical treatment of psoriasis and other conditions, chronic exposure to high levels of arsenic (form unknown) in drinking water, chronic exposure to arsenic trioxide (arsenite) in smelters and pesticide manufacturing plants, and chronic exposure to arsenate and arsenite in pesticide manufacturing plants and to insecticides in vineyards. The Agency concludes that sufficient epidemiological data exists to show that both forms of arsenic act as oncogens in humans and therefore recommends that an RPAR be issued against each inorganic arsenical pesticide.

There are many different tests that show arsenate and arsenite are mutagens (produce heritable genetic change) in bacterial cells, cultured human cells, and in rodents. The effects seen are point mutations (bacterial cells), inhibition of a DNA repair system and of DNA synthesis (cultured human epidermal cells), dominant-lethal effects (mice), chromosome effects such as sister chromatid exchange (cultured human lymphocytes), and translocations, aneuploidy, and chromatid breakage (cultured human leukocytes and lymphocytes). EPA concludes that sufficient data exist to show that both forms of arsenic produce mutagenic effects and therefore recommends that an RPAR be issued against each inorganic arsenical pesticide.

There are numerous studies that show arsenate and arsenite are teratogens (produce birth defects). In these studies, pregnant mice, rats, and hamsters were given arsenic either orally or by injection. Both forms of arsenic produced external body, soft tissue, and skeletal malformations, but arsenite produced these defects at lower doses than arsenate. EPA concludes that there is sufficient evidence that both forms of arsenic display teratogenic effects. Based on the level of exposure of each arsenical pesticide to a 60-kg woman (see Section III), EPA further concludes that an ample margin of safety does not exist for any use of the inorganic arsenicals and recommends that an RPAR be issued against these pesticides.

I. BACKGROUND

A. Chemical/Physical Characteristics

Arsenic occurs in both organic and inorganic forms. Organic arsenic differs from inorganic in that organic forms usually contain carbon (EPA 1976a).

The chemistry of arsenic is complex because arsenic can have multiple valence states. Each valence state of arsenic exhibits distinctly different chemical properties. Arsenic acid, arsenic pentoxide, calcium arsenate, lead arsenate, sodium arsenate, and sodium pyroarsenate are pentavalent arsenicals; ammonium arsenite, arsenic trioxide, copper acetoarsenite, and sodium arsenite are trivalent arsenicals. Knowledge of the conditions that promote interconversions between valence states, particularly those that promote the prevalence of trivalent arsenic, is important in evaluating the environmental effects of arsenic (Oak Ridge 1976).

(1) Pentavalent Arsenicals

(a) Arsenic Acid

Arsenic acid, an inorganic arsenical desiccant and herbicide, is the common name for orthoarsenic acid. The chemical formula is H_3AsO_4; the molecular weight is 151.1; and the density is 2.0 to 2.5 (Meister 1977). It exists as white, translucent crystals at 20°C. The melting point is 35.5°C, and the boiling point is 160°C in the anhydrous state. The solubility of arsenic acid in water is 167 g/liter (Oak Ridge 1976).

(b) Arsenic Pentoxide

Arsenic pentoxide is an inorganic arsenical wood preservative, and an intermediate in the production of metal arsenates. The chemical formula is As_2O_3; the molecular weight is 229.8; and the density is 4.3. It exists as a white, amorphous solid. Arsenic pentoxide decomposes at 315°C and is very soluble in water, 1500 g/liter (Oak Ridge 1976).

(c) Sodium Arsenate

Sodium arsenate is an inorganic arsenical wood preservative and insecticide. The chemical formula is Na_2HAsO_4; the molecular weight is 129.9, and the density is 1.9. It exists as a grey-white powder and is very soluble in water (Oak Ridge 1976).

(d) Sodium Pyroarsenate

Sodium pyroarsenate is an inorganic arsenical wood preservative. The chemical formula is $Na_4As_2O_7$; the molecular weight is 353.79, and the density is 2.2. It exists as white crystals and decomposes at 1,000°C. The melting point is 850°C. It is very soluble in water (Weast 1977).

(e) Lead Arsenate (Standard and Basic)

Lead arsenate, an inorganic arsenical insecticide, is manufactured from arsenic acid, which in turn is made from arsenic trioxide (EPA 1976b). There are two forms of lead arsenate, standard and basic. Standard (or acid) lead arsenate is the common name for acid orthoarsenate ($PbHAsO_4$). Basic lead arsenate is the common name for basic orthoarsenate ($Pb_4(PbOH)(AsO_4)_3$, which exists as a white crystal at 20°C. The molecular weight is 899.4, and the density is 7.8. Its melting point is 1,042°C, and it is very slightly soluble in water (Oak Ridge 1976). Lead arsenate is not decomposed as readily as other arsenicals and is less likely to be phytotoxic (Meister 1977). (See Section I.I for a discussion of the chronic effects of lead.)

(f) Calcium Arsenate

Calcium arsenate is an inorganic arsenical insecticide and herbicide, which, like lead arsenate, is formulated from arsenic acid (EPA 1976b). The chemical formula is $Ca_3(AsO_4)_2$. Its molecular weight is 398.1, and its density is 3.6. Its solubility in water is 0.13 g/liter (Oak Ridge 1976). Calcium arsenate is somewhat unstable. Although it contains no more water-soluble arsenic than lead arsenate when freshly manufactured, the action of carbonic acid and dilute alkaline solutions decomposes calcium arsenate, liberating the water soluble form. As a result, it must be used with quantities of lime to avoid injury to some plants (Meister 1977).

(2) Trivalent Arsenicals

(a) Ammonium Arsenite

Ammonium arsenite (also ammonium metaarsenite) is an inorganic arsenical wood preservative. The chemical formula is NH_4AsO_2; its molecular weight is 125, and the density is 1.3. It forms colorless, hygroscopic rhombic prisms. It is very soluble in cold water and decomposes in hot water (Weast 1977).

(b) Arsenic Trioxide

Arsenic trioxide, an inorganic arsenical rodenticide, is the common name for arsenious (or arsenous) oxide; refined arsenic trioxide is known as white arsenic. The chemical formula is As_2O_3 [also As_4O_6]; the molecular weight is 197.8, and the density is 3.7. Arsenic trioxide exists as an amorphous white powder or vitreous solid with a boiling point of 465°C. It sublimes at 193°C, and its solubility in water is 20.6 g/liter (Oak Ridge 1976).

(c) Sodium Arsenite

Sodium arsenite is an inorganic arsenical herbicide and insecticide (Meister 1977). The chemical formula is $NaAsO_2$. Its molecular weight is 129.9, and its density is 1.9. It exists as a grey-white powder and is very soluble in water (Oak Ridge 1976). Sodium arsenite is the reaction product of arsenic trioxide plus sodium hydroxide.

(d) Copper Acetoarsenite (Paris Green)

Paris green is the common name for copper acetoarsenite, which is formulated from arsenic trioxide (EPA 1976b). The chemical formula is $Cu(C_2H_3O_2)\cdot 3Cu(AsO_2)_2$, and the molecular weight is 586.2. The compound exists as an emerald green powder. It is insoluble in cold water and alcohol, and soluble in acid and NH_4OH (Weast 1977). Although copper acetoarsenite contains the salt of an organic acid, it behaves chemically as an inorganic arsenical (Letter 1975).

B. Formulation and Class

Lead arsenate is an insecticide and is available in dusts, wettable powders, fertilizer mixtures, and baits. Calcium arsenate is an insecticide and herbicide; it is available in dusts, wettable powders, baits, high water suspensions, and granules. Sodium arsenite is a herbicide and insecticide; it is available in aqueous solutions at strengths of 4, 6, 8, and 9 1/2 pounds/gal. Paris green is an insecticide and is available in 5% granules. Arsenic acid is a cotton desiccant and herbicide, available as a 75% water miscible solution. Ammonium arsenite is a wood preservative and is available as a 7.7% pressurized formulation with other ingredients. (Pressurized formulations are manufactured for use in pressurized wood-treatment systems.) Arsenic trioxide is used as a rodenticide and is available as a bait formulation. Arsenic pentoxide and arsenic trioxide are used as wood preservatives and antifouling paints and are available as 1.5 and 37.0% pressurized formulations with other ingredients. Sodium pyroarsenate is a wood preservative and is available as a 6.2% pressurized formulation with other ingredients. Sodium arsenate is an insecticide and wood preservative and is available as a 43% dust, a 2% solution, and 14 to 43.5% pressurized formulations with other ingredients, and 0.7 to 3% baits (Meister 1977; EPA 1975).

C. Registered Uses and Production

Several inorganic arsenicals have long been used as pesticides. Copper acetoarsenite was used against the potato beetle in the Rocky Mountain region as early as 1865. Lead arsenate was introduced as an insecticide against the gypsy moth in Massachusetts in 1892. Sodium arsenite was used both as an insecticide and as a weed killer (HEW 1969).

Table 1 shows the number of companies holding Federal registrations for the various inorganic arsenicals or who have state registrations for such pesticides, and filed timely applications for federal registration pursuant to 40 CFR 162.17.[1/]

Table 1.

Registration	Product	Companies	Products
Federal	Standard Lead Arsenate	23	53
State	Standard Lead Arsenate	5	6
Federal	Basic Lead Arsenate	3	3
State	Basic Lead Arsenate	1	1
Federal	Copper Acetoarsenite	7	11
State	Copper Acetoarsenite	1	1
Federal	Calcium Arsenate	17	32
State	Calcium Arsenate	2	3
Federal	Sodium Arsenite	58	75
State	Sodium Arsenite	9	10
Federal	Ammonium Arsenite	2	2
Federal	Arsenic Trioxide	19	24
State	Arsenic Trioxide	3	5
Federal	Sodium Arsenate	15	20
State	Sodium Arsenate	2	2
Federal	Arsenic Acid	9	18
Federal	Arsenic Pentoxide	5	14
State	Arsenic Pentoxide	2	2
Federal	Sodium Pyroarsenate	1	1

1/ Prior to the enactment of the 1972 ammendments to FIFRA, federal registration was required only to ship or distribute a pesticide in interstate commerce. The 1972 ammendments to FIFRA extended the federal registration requirement to products in intrastate commerce. In implementing the 1972 ammendments, EPA permitted persons with valid state registrations to continue to sell and distribute their products, provided that timely application for federal registration was filed, and that other requirements set out in 40 CFR 162.17 were satisfied.

A total of 283 inorganic arsenic products are registered under Federal and state regulations. A registrant who has registrations for more than one type of arsenic (or who holds both Federal and state registrations for one or more types of arsenic) would be listed more than once.

Approximately 69% of all arsenic and its inorganic compounds produced in the U.S. is used for insecticides and herbicides. Over half of this amount is used by the cotton production industry as herbicides and desiccants for the preparation of cotton prior to machine picking. Another 7% of the total production is used as wood preservatives (OSHA 1977).

Most domestic arsenic production is in the form of arsenic trioxide which is derived from collected flue dusts from copper smelting. Since 1959, the entire U.S. production of arsenic trioxide has been at the Tacoma, Washington plant of the American Smelting and Refining Company (EPA 1976b). Arsenic trioxide is used to manufacture approximately 97% of other arsenic end-products (OSHA 1977). Since there is a single manufacturer for this material, recent production figures cannot be released. Section 7(c) of FIFRA requires manufacturers and formulators to submit to the U.S. Environmental Protection Agency (EPA) information on the production, sales, and distribution of their pesticide products. This information is confidential and may be released only in accordance with the procedures outlined in Section 7(d) and 10 of FIFRA. A confidential memorandum summarizing this information has been sent to the Deputy Assistant Administrator for Pesticide Programs (Memo 1978a). Production figures are available, however, through 1968. For the ten-year period 1958 through 1968, production of arsenic trioxide averaged 4,745 metric tons/year.[2/] The lowest production figure was 2,340 metric tons/year in 1959, and the highest was 7,000 metric tons/year in 1965 (EPA 1976b).

From 1965 through 1972, the average consumption of lead arsenate as an insecticide on crops and for other uses was 3,500 metric tons/year, or 1,100 metric tons/year in equivalent arsenic trioxide; for calcium arsenate, the figures were 900 and 450 metric tons/year, respectively; and for copper acetoarsenite, they were 7,300 and 4,000 metric tons/year, respectively (EPA 1976b).

Use of arsenic acid as a desiccant on cotton has increased steadily since the late 1960s, from 965 metric tons/year in 1968 to 4,400 metric tons/year in 1974 (EPA 1976b).

[2/] A metric ton equals 1,000 kilograms or 2,204.62 pounds.

The "National Study of Agricultural, Governmental and Industrial Uses of Pesticides" (Memo 1977c), conducted by EPA's Human Effects Monitoring Branch, provided data on the patterns of use of the following inorganic arsenicals for 1974: for calcium arsenate, 1,840 pounds active ingredient (AI) were used in agriculture on fruit and nuts, 446 pounds AI in government (use by Federal, state, and local governments), and 33 pounds AI in industry (use by pest control operators, utility companies, etc.); for copper acetoarsenite, 18,998 pounds AI were used in government, and 50 pounds AI in industry; for lead arsenate, 53,627 pounds AI were used in industry, 2,106 pounds AI in government, and a total of 333,788 pounds AI in agriculture (333,329 pounds on fruit and nuts, and 459 pounds on ornamentals and miscellaneous); for sodium arsenite, 20,287 pounds AI were used in government, 237,820 pounds AI in industry, and a total of 86,660 pounds AI in agriculture (57,344 pounds on fruit and nuts, and 29,316 pounds on ornamentals and miscellaneous).

The National Soils Monitoring Program (Memo 1977a), conducted by EPA's Ecological Monitoring Branch, has collected data on the application of inorganic arsenicals to various representative cropland sampling sites through 1974. The data indicated a limited use (<1%) of inorganic arsenicals (Table 2). Among the crops to which these inorganic arsenicals were applied were grapes, apples, oranges, peaches, potatoes, dewberries, and cotton.

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Table 2.

Compound	Fiscal Year	Sites Sampled	% Sampled	Avg Total Application (pounds/acre
Calcium Arsenate	1970	1/1,346	0.07	9.8
Sodium Arsenite	1969	4/1,684	0.24	5.25
	1974	1/1,165	0.1	10.5
Lead Arsenate	1969	1/1,684	0.06	3.8
	1970	1/1,346	0.07	6.4
	1972	3/1,473	0.2	7.07
	1973	1/1,402	0.1	4
	1974	1/1,165	0.1	7.68
Arsenic Pentoxide	1972	2/1,473	0.14	0.5

D. Tolerances

Copper acetoarsenite, ammonium arsenite, sodium pyroarsenate, arsenic pentoxide, and arsenic trioxide have no agricultural uses.

(1) Arsenic Acid

A tolerance for residues of orthoarsenic acid (arsenic acid) is listed in 40 CFR 180.180 as follows: 4 ppm (as combined AS_2O_3) in or on the raw agricultural commodity cottonseed.

(2) Calcium Arsenate

A tolerance for total residues of calcium arsenate is listed in 40 CFR 180.192 as follows: 3.5 parts per million (ppm) of combined As_2O_3 in or on asparagus, beans, blackberries, blueberries (huckleberries), boysenberries, broccoli, brussels sprouts, cabbage, carrots, cauliflower, celery, collards, corn, cucumbers, dewberries, eggplants, kale, kohlrabi, loganberries, melons, peppers, pumpkins, raspberries, rutabagas (with or without tops) or rutabaga tops, spinach, squash, strawberries, summer squash, tomatoes, turnips (with or without tops) or turnip greens, and youngberries.

(3) Lead Arsenate

Tolerances for total residues of lead arsenate are listed in 40 CFR 180.194 as follow: 7 ppm of combined lead in or on apples, apricots, asparagus, avocados, blackberries, blueberries (huckleberries), boysenberries, celery, cherries, cranberries, currants, dewberries, eggplants, gooseberries, grapes, loganberries, mangoes, nectarines, peaches, pears, peppers, plums (fresh prunes), quinces, raspberries, strawberries, tomatoes, and youngberries; and 1 ppm of combined lead in or on citrus fruits.

(4) Sodium Arsenate

A tolerance for residues of sodium arsenate (combined As_2O_3) is listed in 40 CFR 180.196 as follows: 3.5 ppm in or on grapes.

(5) Sodium Arsenite

Tolerances for residues of sodium arsenite (expressed as As_2O_3) resulting from dermal application to animals under the supervision of the U.S. Department of Agriculture (USDA) are listed in 40 CFR 180.335 as follow: 2.7 ppm in kidney and liver of cattle and horses; and 0.7 ppm in the meat, fat, and meat byproducts (except kidney and liver) of cattle and horses.

USDA will issue a certificate to the owner of the animals showing the composition of the pesticide formulation and dates of treatment, and also specifying a minimum preslaughter interval of 14 days. In addition, 40 CFR 180.319 lists an interim tolerance for sodium arsenite of 0.05 ppm on grapes.

E. Fate in the Biological Environment

(1) Absorption

(a) Microorganisms

Microorganisms take up arsenates and arsenites via the phosphate transport system. Both arsenate and phosphate have an affinity for the transport system of yeast. Rothstein (1963) showed arsenate was taken up rapidly by bakers' yeast cells, but uptake then decreased and stopped within 40 minutes. Although arsenate and phosphate competed for the same transport system, phosphate was taken up twice as fast. Button and Dunker (1971) found that marine yeast accumulated arsenate and phosphate through the same active transport system. Arsenate inhibited phosphate transport, and phosphate competitively reduced arsenate uptake.

Arsenic transport into bacterial cells (*Escherichia coli*) also involves the phosphate transport system. Bennett and Malamy (1970) found that a wild type of *E. coli* took up labeled arsenate in the absence of inorganic phosphate. If phosphate was then added, there was a rapid efflux of previously accumulated arsenate.

(b) *Plants*

Plants can absorb arsenical compounds from soil, water, and air through stomates, the cuticle (slow action), and cell membranes of roots, shoots, and coleoptiles. Exposure of plants to arsenic is from polluted air, pesticide-contaminated soil and water, and from naturally occurring deposits. Arsenic uptake is influenced by factors such as plant species, arsenical form, soil type, organic matter content, and ions present in soil (P, Ca, Al, Fe, Se, S). [See also Section I.E.(4)].

Sachs and Michael (1971) studied absorption of inorganic arsenic (sodium arsenite, sodium arsenate) and of organic arsenic (cacodylic acid, monosodium methane arsonate) by bean roots (*Phaseolus vulgaris*). When foliarly applied,

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organic forms were translocated through the plant, while the inorganics were not. Both inorganic forms were more rapidly absorbed by bean roots than were the organics.

Soils have widely differing characteristics such as pH, oxide content, organic matter, and texture that affect the level of water-soluble arsenic in the soil (Walsh and Keeney 1975) [see also Section I.F.(1)(a)]. Woolson et al. (1971b) reported that the chemical form and solubility of the soil arsenic have more impact on plant growth than the total arsenic content of the soil. Translocation of arsenic is more extensive in warmer temperatures for most plant species.

The uptake of arsenic by plants (Table 3) is influenced by the soil elements and the plant species (Oak Ridge 1976). There is also competition between arsenic and phosphorous [see Section I.F.(1)(a)]. Rumburg et al. (1960) found that increasing the concentration of phosphorous in a nutrient solution decreased the amount of arsenate taken up by Clinton oats (Avena sativa). Jacobs and Keeney (1970) reported that phosphorus levels had little effect on uptake of arsenic by corn (Zea mays) grown in Waupun silt loam (80 ppm arsenic).

Table 3. Effects of Other Elements on Uptake of Arsenic by Plants

Plant	Other element	Effect of other ion on arsenic concentration	Reference
Clinton oats (*Avena sativa*)	Phosphorus	Decrease	Rumburg et al. (1960)
Corn (*Zea mays*)	Phosphorus	Increase in sand, little effect in silt loam	Jacobs and Keeney (1970)
Tobacco (Hicks variety)	Phosphorus	Increase	Small and McCants (1962)
Corn (*Zea mays*)	Calcium	Decrease	Woolson (1972)
Barley	Calcium	Little or no effect	Vandecaveye et al. (1936)
Plants (in general)	Aluminum	Decrease	Walsh and Keeney (1975)
Barley	Iron	Decrease	Vandecaveye et al. (1936)
Potatoes	Iron	Decrease	Steevens et al. (1972b)
Tobacco (Hicks variety)	Iron	Decrease	Small and McCants (1962)
Grasses, sunflower	Selenium	No correlation	Olson et al. (1940)
Rice	Sulfur	Decrease	Epps and Sturgis (1939)

(c) Animals

Insects, aquatic organisms, birds, and mammals generally take in arsenic by ingestion.

The manner of arsenic uptake by marine organisms is unknown (Penrose 1974). Fish feeding on arsenic-containing organisms probably obtain some arsenic by ingestion. Arsenic may be absorbed by crustaceans and by fish through the gills, as are other metals in the aquatic environment. Inorganic arsenic may be taken in with food and metabolized to water-soluble and lipid-soluble organoarsenical compounds (Schuth et al. 1974). Inorganic arsenic in water may be directly absorbed by fish.

Arsenic has been found in fish and aquatic invertebrates in both fresh and salt water [see Section I.E.(4)]. Aquatic organisms bioaccumulate arsenic but do not biomagnify it (Woolson 1975). They apparently are able to eliminate arsenic at approximately the same rate as it is ingested. In some cases, however, arsenic is found at higher concentrations in organisms than in the surrounding water. Gilderhus (1966) exposed bluegills to various concentrations of sodium arsenite. Arsenic residues were found in all tissues analyzed. Arsenic levels in fish increased during the exposure period and were higher in fish than in the water at the end of exposure.

Arsenic uptake by wild birds is primarily through ingestion of feed contaminated with residues of arsenical pesticides (Oak Ridge 1976).

Almost all arsenic uptake by mammals is through ingestion. Wildlife can take in arsenic by feeding in areas that have been contaminated with arsenical herbicides. Arsenic can also be absorbed through skin abrasions in sheep, cattle, and horses (Case 1974). Studies in mammals indicate that absorption of inorganic arsenic through the gastrointestinal tract can result in alteration of the chemical form (i.e., by methylation) before it reaches the general circulatory system and other organs.

(d) Humans

Arsenic can enter the body by ingestion, inhalation, and absorption through the skin. Several factors affect absorption, such as water solubility, lipid-solubility, type of arsenical, and area of absorption. Skin absorption is also dependent on the lipid-solubility of the compound. Lipid-insoluble arsenic salts are capable of combining with fatty acids in the skin to form lipid-soluble metal oleates which the skin is capable of absorbing (Rothman 1954). Oehme (1972) reported that inorganic arsenic is absorbed significantly through intact skin. Trivalent arsenicals are generally absorbed through the skin more readily than the pentavalent forms. Pentavalent inorganic arsenicals are better absorbed than trivalent forms in the digestive tract, probably because they react less with the intestinal contents and mucosa (Harvey 1975).

(2) Distribution

(a) Plants

Plant roots usually have the highest content of arsenic; vegetative growth has an intermediate level; and edible seeds of fruits contain the lowest levels (Walsh and Keeney 1975).

Machlis (1941) grew Sudan grass (*Sorghum vulgare, var. sudanense*) and bush bean (*Phaseolus vulgaris var. humilis*) in the greenhouse for varying lengths of time in nutrient solutions containing various concentrations of sodium arsenite. Leaves contained the highest arsenic concentrations, stem tissues contained an intermediate amount, and reproductive structures contained the least amount of arsenic. Concentrations many times greater than those of the leaves or nodes were observed in Sudan grass roots after they were placed in arsenic-containing nutrient solutions for one week (1 to 18 ppm arsenic in solution resulted in 338 to 1,461 ppm arsenic in roots). Sudan grass was more arsenic-resistant than the sensitive bean species.

Watanabe et al. (1971) reported that low levels (<0.10 ppm) of arsenic were detected in fruit from eggplant grown in soil treated with 20 ml of arsenious acid (equivalent to 20 mg of arsenic per plant). Roots and leaves showed the highest arsenic concentrations (1.35 and 0.85 ppm, respectively) when 12.0 ppm arsenic was found in the upper layer of the soil.

Geisman et al. (1969) determined the concentration of arsenic in tomato plants grown under greenhouse conditions in soils that had been treated for at least two years with a sodium arsenite solution. Plants were grown on treated and drift portions of the plot and untreated controls were grown in a separate area. Table 4 shows that the highest arsenic concentrations were found in the roots and the lowest concentrations were found in the fruit.

Table 4. Average Arsenic Concentrations Found in Treated and Untreated Soil and Plant Samples (dry weight basis)

	Average Arsenic Concentration (ppm)[a]			
Treatment	Soil	Roots	Stems and Leaves	Fruit
Untreated	<0.2	<0.2	<0.2	<0.2
Drift	331.0	400.0	187.0	<0.2
Treated	654.0	1707.0	334.0	1.4

[a] Data from Geisman et al. (1969).

Experiments with the lowbush blueberry (*Vaccinium angustifolium*) grown in commercial and virgin soils revealed a correlation between soil arsenic and arsenic in plant tissue (Anastasia and Kender 1973). Arsenic trioxide solutions of various concentrations were used to irrigate the soil. Analysis of arsenic content of leaves, stems, and roots indicted that roots absorb and translocate arsenic into the aerial organs (see Table 5). The greatest arsenic concentration was found in roots; stem concentration was slightly higher than leaf concentration. Tissue arsenic concentration increased as soil arsenic increased.

Table 5. Arsenic Accumulation in Leaves, Stems, and Roots of Lowbush Blueberry Plants Grown at Five Arsenic Levels in the Greenhouse for 17 Weeks[a]

Total soil arsenic (ppm)	Arsenic content (ppm) Leaves	Stems	Roots
7.7 (control)	0.78	0.27	2.40
17.1	3.55	3.95	50.02
43.8	6.74	7.58	93.72
69.5	8.14	11.64	121.28
84.5	14.97	13.33	164.22
LSD (0.05)[b]	5.05	6.03	43.53

[a] Mean of three clones; data from Anastasia and Kender (1973).

[b] Test for significance of mean differences.

(b) Humans and Animals

According to Webb (1966), four major factors influence distribution of arsenic in animals: type of arsenical, animal species, route of administration, and time after administration.

With the exception of the rat, inorganic arsenic injected into mammals tends to concentrate in the solid tissues more than in the blood. Generally, the highest concentrations are in the liver, kidney, spleen, and lung. Trivalent arsenic will bind to sulfhydryl groups in animal tissue and slowly be released, while pentavalent forms are rapidly eliminated via the feces and urine. High concentrations of arsenic are found in hair and nails because it reacts with the sulfhydryl groups in the keratin (Harvey 1975).

Arsenic is a normal environmental contaminant and is always present in human tissues (Rentoul and Smith 1973). The total arsenic content of a normal adult body is estimated to be 14 to 21 mg (Harvey 1975).

In a study by Mealey et al. (1959), eleven patients dying of intracranial disease were given radioactively labeled trivalent arsenic intravenously. In a post-mortem examination, organs and tissues were analyzed for activity. The liver, kidneys, and spleen were the primary sites of arsenic accumulation.

In guinea pigs, rabbits, apes, and humans, radioactively labeled potassium arsenite was injected subcutaneously and was distributed primarily in skeletal muscles (Hunter et al. 1942).

Ducoff et al. (1948) studied the distribution of arsenic residues in various species of mammals, including humans, with radioactively labeled sodium arsenite (^{74}As). Eight Sprague-Dawley male rats were injected intravenously with 47 microcuries (uCi) each and were sacrificed in pairs at 6, 24, 48, and 96 hours. The authors noted the high concentration of arsenic in the blood, fairly high arsenic content of lung and spleen, the large individual variation, and the lack of any great tendency for a decline in the arsenic content of most tissues. The distribution of arsenic residues in four rabbits showed that concentrations of arsenic in blood at any time interval were never as great as in most solid tissues, that all tissues showed a distinct reduction in arsenic content over time, and that liver, kidney, and lungs contained the highest concentrations of arsenic.

The same authors also studied arsenic distribution in mice and humans. In a study on mice, 19 males of the A strain, 11 bearing lymphomas that had been transplanted three weeks previously, were injected intraperitoneally with 0.8 uCi radio-labeled sodium arsenite each. Arsenic concentration was determined in tissue samples of kidney, liver, lung, spleen, muscle, and tumor (when these were present). The ratio of arsenic concentration in kidney, liver, and spleen of healthy inbred mice was found to be fairly constant for a given time after administration. Using this ratio as a criterion, it was found that arsenic distribution in tissues was altered unpredictably by the presence of transplanted tumors.

In the residue study on humans, a moribund 65-year-old female with carcinoma of the parotid (salivary gland) was given 500 microcuries (uCi) of ^{76}As (equivalent to 4 mg arsenic) 20 hours before death. The tissue distribution (in uCi/g) at time of death was as follows: liver, 46.4; kidney, 29.5; spleen, 16.1; parotid tumor, 15.6; heart, 14.6; heart, 14.6; jejunum, 14.3; vertebral marrow, 14.2; mesenteric lymph node, 12.8; stomach, 11.7; pancreas, 11.6; muscle (quadriceps), 11.4; ileum, 11.1; lung, 10.8; femoral marrow, 10.8; adrenal 8.5; ovary, 8.3; thyroid, 7.6; skin, 6.7; brain, 2.5; and femoral cortical bone, 2.4.

In livers of fish from the Great Lakes, Lucas et al. (1970) found concentrations of arsenic ranging from 5.6 to 80 ppb. The arsenic was primarily in the fat fraction of the liver and other organs. Fish generally contain lower arsenic levels than other aquatic organisms (Lunde 1970).

(3) Excretion and Degradation in Animals

Webb (1966) has noted that arsenicals are excreted at different rates, depending on the valence state. The pentavalent arsenicals are usually excreted rapidly by the kidney since they do not bind readily to tissues, whereas the trivalent arsenicals become rapidly bound and are excreted only as fast as they are released.

Mealey et al. (1959) suggested that arsenite administered intravenously into humans is excreted in three phases. More than 99% of a radio-labeled dose of sodium arsenite was excreted within 15 hours after administration. Labeled arsenic was excreted at a low, constant rate over the next 155 hours, and the remainder was removed at an even lower rate. Chemical tests of the urine indicate that the labeled arsenite is recovered as a mixture of arsenite and arsenate, the latter predominating.

Winkler (1962) showed that rats fed either sodium arsenite or sodium arsenate excreted primarily pentavalent arsenic, indicating in vivo oxidation of arsenite.

Harvey (1975) states that trivalent arsenic is slowly excreted in the urine and that this is the basis for its cumulative toxic action. Arsenate forms are rapidly excreted in humans and therefore little arsenic accumulates.

Coulson et al. (1935) studied the excretion of shrimp-arsenic (an organo-arsenical found in shrimp) in comparison to that of inorganic arsenic trioxide (trivalent arsenical) in rats and humans. The "normal" level of arsenic excretion was determined for rats. Two groups of rats given a stock (no arsenic) diet excreted an average of 0.0059 and 0.0065 mg arsenic, respectively, in the urine (80%) and feces (20%). Rats in the first group were then fed a diet containing shrimp-arsenic for one day. Within four days, 74.6% of the arsenic had been recovered, and arsenic excretion fell to normal levels. The second group, however, which consumed a diet containing arsenic trioxide, eliminated only 19.1% of the ingested dose before arsenic excretion fell to normal levels; 80% was retained in the body. The experiment was repeated one week later with the first group of rats receiving the inorganic arsenic and the second receiving the organic shrimp-arsenic; the results were the same.

The same authors conducted a similar experiment on two humans. When the two subjects were given shrimp-arsenic in their diet, the rate of elimination was about the same as in the rat. When inorganic arsenic (As_2O_3) was added to the diet, it was excreted more slowly than the shrimp arsenic had been but was eliminated more completely than in rats.

Peoples (1964) studied the rate of urinary excretion of arsenic acid, a pentavalent arsenical, in cattle. Two animals received daily doses of 11.6 mg arsenic acid in the feed supplement for seven weeks;

two received 58.2 mg; and two received 291.0 mg. After seven weeks, the two low-dose animals had excreted 76 and 86% of the total arsenic ingested; the two mid-dose animals had excreted 79 and 58%; and the two high-dose animals had excreted 54 and 98%. The author suggested that the high levels of excreted arsenic indicated there is little arsenic storage in cattle tissue. The author indicated that preliminary studies showed that the tissue-bound arsenic was entirely pentavalent with no evidence of reduction to the trivalent form.

Lakso and Peoples (1975) fed sodium arsenate and sodium arsenite to cows and dogs for five consecutive days. Regardless of the arsenic form ingested, both animals excreted approximately equal amounts of methylated and inorganic arsenic. Crecelius (1977b) observed similar results when studying changes in the chemical speciation of arsenic following ingestion by man (see Section I.J).

Ginsburg (1965) reported that arsenate, given intravenously to dogs, was reabsorbed by the proximal renal tubule and reexcreted as arsenite (see Section I.J).

Ducoff et al. (1948) studied the excretion of radio-labeled sodium arsenite (a trivalent arsenical) in rats, rabbits, and humans. Five male Sprague-Dawley rats were each injected with 47 microcuries (uCi) of radio-labeled sodium arsenite (^{74}As); four rabbits were each injected with 235 uCi, and 2 human subjects were injected with 3.0 and 2.7 millicuries, respectively. The results showed that, during comparable time intervals, arsenic excretion took place more slowly in the rats (<10% during the first 48 hours) than in rabbits (about 70%) or humans (about 30 to 45%). The authors also noted that the arsenic content of rats rapidly reached equilibrium. For all species, less than 10% of the excreted arsenic was found in the feces.

Fairhall and Neal (1938) studied the excretion of lead arsenate, a pentavalent arsenical, in two human subjects. After a preliminary period of three days on a controlled diet, both subjects received 10 mg of lead arsenate daily for ten days. Arsenic residues in urine and feces were measured for 23 days starting with the first day of exposure. The results showed that the arsenic was eliminated only through the kidneys. (Total arsenic residues in feces were only a few hundredths of a milligram.) About 96.4% of the arsenic was excreted in urine in the first subject, and about 77.5% in the second. The authors interpreted the immediate excretion of most of the ingested arsenic as evidence that lead arsenate dissociates in the gastrointestinal tract, even though its solubility in water is low.

Webster (1941) studied the excretion of lead arsenate in nine adult male orchardists who customarily ate unwashed apples treated with lead arsenate. During the 10-to-12-day experimental period, the subjects ate their usual number of treated apples (average, three apples) from separately provided lots. Analyses of samples of fruit eaten by the men showed a potential arsenic intake of 1 to 25 mg of lead and 0.34 to 6.8 mg of arsenic per person per day. A portion of each day's urine and the total daily feces were analyzed for arsenic residues. The average arsenic residues for all nine persons over the experimental period was 0.019 mg in urine and 2.86 mg in feces. The total fecal arsenic was about 15% greater than the total urinary arsenic. The author compared this result with that obtained by Fairhall and Neal (1938) and suggested that the different results were caused either by differences between the chemical and physical properties of weathered spray residue and pure lead arsenate, or by differences in excretion of arsenic by persons having chronic exposure and those having acute exposure.

(4) Bioaccumulation and Biomagnification

The terms bioaccumulation and biomagnification are not treated consistently in scientific literature and are sometimes used interchangeably. For purposes of this document, however, bioaccumulation means the accumulation or concentration of pesticide residues in individual organisms or in individual species. Biomagnification, on the other hand, means the transference of pesticide residues from lower to higher organisms in the food chain, resulting in greater (magnified) concentrations of pesticide residues in higher organisms than were present in the lower forms.

Arsenic does not appear to biomagnify through the food chain (Oak Ridge 1976).

Arsenic does not continuously accumulate in mammalian tissues because it apparently reaches dynamic equilibrium between intake and excretion (Frost 1967). Variations in the excretion rates of the different arsenicals by mammals are believed to be the basis for the varying toxicities (Frost 1967). The average human body burden of arsenic in normal adults is 14 to 21 mg (Harvey 1975); this arsenic is stored primarily in the liver, kidney, wall of the gastrointestinal tract, spleen, and lung, while smaller amounts are found in the muscle and nervous tissue. High levels of arsenic are also found in human hair and nails due to the high sulfhydryl content of keratin.

Since arsenic occurs naturally in aquatic systems, many aquatic organisms tend to bioaccumulate it. Due to the higher concentration of arsenic in salt water, marine organisms (plant and animal) tend to accumulate arsenic to a greater extent than freshwater forms (Woolson 1975). The highest rates of arsenic accumulation are found in aquatic plants (Woolson 1975). The lower aquatic organisms usually have the highest arsenic residues. Sohacki (1968) found plankton to be an effective accumulator of arsenic. Schuth et al. (1974) showed that there was greater arsenic accumulation by aquatic organisms such as algae and duckweed (lower level of food chain) than in fish and crayfish (upper level of food chain). In a review of the literature, Schroeder and Balassa (1966) reported that levels of arsenic are much higher in marine plants and animals than in terrestrial forms.

Ullmann et al. (1961) studied arsenic bioaccumulation by fish in Findley and Chautauqua Lakes in New York, which were treated annually since 1956 with sodium arsenite for weed control. Detectable quantities of arsenic were found in the fillets (including skin) of all fish from Findley Lake, ranging from 0.27 to 0.47 ug/g. Seven of eight fish contained arsenic in the viscera (including bone and scales), ranging from 0.10 to 0.78 ug/g. No significant differences occurred between fish taken before or after spraying in either of the treated lakes. The fish from Chautauqua Lake contained less arsenic than those from Findley. Nine of 20 fish contained arsenic in the fillets ranging from 0.10 to 0.28 ug/g. Seven contained arsenic in the viscera ranging from 0.10 to 0.29 ug/g. These values were only slightly higher than those obtained in the ten control fish from untreated (control) Cassadaga Lake. Six of these contained from 0.10 to 0.12 ug/g in the viscera, and five contained from 0.10 to 0.14 ug/g in the fillets.

Terrestrial plants can bioaccumulate arsenic [see Section I.E.(2)(a)]. Since most plants are sensitive to arsenic, there is a reduction in growth before a high level of arsenic can occur (Walsh and Keeney 1975). [See also Sections I.E.(2)(a) and (6)].

Plants growing near a copper smelter were found to contain increased arsenic levels as a result of soil contamination with arsenic (Crecelius et al. 1974). Porter and Peterson (1975) measured the arsenic content of plants grown in contaminated soils (i.e., mine tips, and areas of smelter waste). The foliage of several species contained 460 to 6,640 ppm, while plants in areas away from the smelter contained 0.28 to 0.33 ppm of arsenic.

(5) Biotransformation

In soil, sediment, and water, transformation is usually mediated by microorganisms. Various fungi and bacteria, under aerobic and anaerobic conditions, can metabolize arsenate and arsenite to volatile arsenicals, usually to di- or trimethyl arsine (Braman 1975; Walsh and Keeney 1975). The trivalent form of arsenic does not persist for long periods in well-aerated soils with significant biological activity (Walsh and Keeney 1975).

Limnetic and marine unicellular algae were able to synthesize fat- and water-soluble arseno-organic compounds from inorganic arsenic ions added to growth media (Lunde 1973b). A greater quantity of lipid-soluble organic compounds were synthesized in cultures with arsenate compared to those with arsenite.

Lunde (1969; 1972; 1973a; and 1973b) has demonstrated that arsenic is present in algae, fish, benthic organisms, and phyto- and zooplankton as water-soluble and lipid-soluble arseno-organic compounds. Studies indicate that arsenate is not a major form of arsenic in aquatic organisms (Woolson 1975).

Several studies of arsenic transformation in humans and animals have been done (see Sections I.E.(3) and I.J). Since the valence state of arsenic largely determines its toxicity, knowledge of the conversion *in vivo* is important. Most authors generally agree that trivalent arsenic is oxidized in tissues and excreted (at least in urine) in a pentavalent form; the reverse transformation, reduction of pentavalent arsenic, is not the favored reaction (see Section I.J).

(6) Other Biological Aspects

(a) Beneficial Effects in Mammals

Arsenic in small amounts may be essential and beneficial to cell metabolism. Attempts to confirm this have been hindered by the ubiquity of arsenic, which makes it difficult to obtain arsenic-free diets.

Muth et al. (1971) found that the addition of 1 ppm of sodium arsenate to selenium-deficient food reduced the incidence of myopathy in lambs. However, attempts have failed to show beneficial effects of arsenic in other selenium-deficiency diseases.

Nielsen et al. (1975) found symptoms of arsenic deficiency in rats fed a diet containing only 30 ppb of arsenic. Male rats had rough haircoats, a low rate of growth, splenomegaly, decreased hematocrit, and increased osmotic fragility of red blood cells. Anke et al. (1976) found similar deficiencies in goats and laboratory pigs fed diets containing less than 50 ppb of arsenic. Compared to the control animals that received food supplemented with 350 ppb of arsenic, the experimental animals had impaired reproductive performance, decreased fetal weights, and increased neonatal mortality.

(b) Phytotoxicity

For many years, inorganic arsenicals have been used as pesticides, herbicides, and plant defoliants. As a result, plant growth has been reduced in some areas previously used for orchards and cotton fields (Walsh and Keeney 1975).

An example of severe phytotoxicity due to arsenic accumulation in the soil occurs in old orchard fields which are recycled for other crop uses (Bishop and Chisholm 1962; Vandecaveye et al. 1936). Some orchards have received over 1,000 kg/ha of arsenic while only 10 kg/ha were used as a defoliant in potato fields (Walsh and Keeney 1975).

Symptoms of arsenic phytotoxicity may vary with the plant variety, type of arsenical, method of application, and environmental conditions (Woolson et al. 1971b) [see also Section I.E.(1)(b) and I.F.(1)(a)]. Young tissue is generally more susceptible to injury than older tissue. Trivalent forms are more toxic than pentavalent forms and can bind with sulfhydryl groups, thus interfering with many enzymatic reactions. Arsenites usually produce rapid contact injury to membranes, which results in rapid water loss. Arsenates cause more subtle symptoms (chlorosis, but not loss of turgor), uncouple oxidative phosphorylation, and stimulate respiration. They may react in the place of phosphates in many reactions (Ashton and Crafts 1973).

Reduced plant growth in corn (Zea mays) was associated with high concentrations of available arsenic in the soil (Woolson et al. 1971b). The authors indicated that the phytotoxicity of arsenic was influenced more by chemical form than by amount. Water-soluble arsenic was more toxic than water-insoluble arsenic. Reduced phytotoxicity occurred in soils containing arsenic and high levels of reactive aluminum versus soils containing arsenic and low levels of reactive aluminum.

Other studies have shown that arsenic can retard plant growth and transpiration (Kerr 1941; Morris and Swingle 1927; and Woolson 1973).

Table 6 gives the toxic levels of soluble arsenic for various crops.

Table 6. Toxic Levels of Soluble Arsenic to Various Crops and Vegetables

Plant	Toxic level Soluble As (ppm)	Reference
cowpeas	1	Albert and Arndt (1931)
barley	2	Vandecaveye (1943)
snap beans	2.5 a/	Jacobs et al. (1970)
peas	2.5	Jacobs et al. (1970)
	9 a/	Bishop and Chisholm (1962)
alfalfa	3.4-9.5	Vandecaveye et al. (1936)
soybeans	3-12	Deuel and Swoboda (1972)
rice	7	Epps and Sturgis (1939)
cotton	8-28	Deuel and Swoboda (1972)
beans	9	Bishop and Chisholm (1962)
corn	20 a/	Jacobs et al. (1970)
potatoes	37 a/	Jacobs et al. (1970)
green beans	10-50	Woolson (1973)
lima Beans	10-50 a/	Woolson (1973)
spinach	10-50 a/	Woolson (1973)
tomatoes	50 a/	Woolson (1973)
radish	40-100 a/	Woolson (1973)
lowbush blueberry	84.5	Anastasia and Kender (1973)
cabbage	100 a/	Woolson (1973)

a/ Level which produces 50 percent yield reduction.

(c) Beneficial Effects in Plants

Although arsenic is not an essential plant nutrient, relatively high arsenic concentrations in soil may have beneficial effects on plant growth (Walsh and Keeney 1975). Stewart and Smith (1922) found that a concentration of 25 ppm in soil enhanced the growth of peas, radishes, wheat, and potatoes. However, beans showed a steady decrease in growth as the arsenic content increased. MacPhee et al. (1960) reported increased turnip yields in soil with a total arsenic content of 126 ppm. The increase in yield was attributed to control of the turnip root maggot. There was a decrease in the yield of other crops such as peas and beans.

There have been beneficial effects on several crops in fields treated with high concentrations of calcium arsenate. Decreased yields for vetch, oats, and barley were first noted in soil with total arsenic concentrations of 94, 138, and 283 ppm, respectively [calcium arsenate applied at 500, 1,000, and 1,500 pounds/acre] (Cooper et al. 1931). When calcium arsenate was applied below these levels, the treated soil had a higher yield than the untreated soils. In another study, corn, sorghum, soybeans, and cotton showed yield increases from applications of 188 ppm [1,000 pounds/acre] (Cooper et al. 1932).

Woolson et al. (1971a) postulated that the stimulation of growth in plants by small amounts of arsenic may be similar to that of other pesticides (e.g., 2,4-D) at sublethal dose levels.

F. Fate in the Physical Environment

(1) Distribution

(a) Soil

Arsenic occurs as a natural constituent in almost all soils. The earth's crust has an estimated background arsenic concentration of 6 ppm [range of 0.1 to 40 ppm] (Bowen 1966). Although there are several sources of inorganic arsenic (i.e., natural weathering of arsenic-containing rock, smelters, volcanic debris, and pesticides), residues from pesticides are a major source of arsenic pollution (Woolson 1976). They are also the major source of arsenic emitted to the environment, but the use of these products is now declining for various reasons (Sullivan 1969). Thirty-two percent (32%) of the total emissions in the U.S. of arsenic are from pesticide use (Duncan et al. 1973).

Williams and Whetstone (1940) sampled soils which had not been contaminated with arsenical pesticides. All samples contained from 0.3 to 38 ppm of arsenic (30% contained less than 5 ppm; 50%, 5 to 10 ppm; and 20%, greater than 10 ppm). Jones and Hatch (1945) compared four plots of soil, arsenic-treated and untreated, after 20 to 25 years of pesticide spraying. The arsenic content was 20 to 30 times the original level. Woolson et al. (1971a) surveyed soils in the U.S. with a history of arsenic treatment. The overall average residue level was 165 ppm, while in control soils it was 13 ppm.

Walsh and Keeney (1975) summarized the arsenic levels for treated and untreated soils in parts of North America. Untreated soils had an arsenic range from undetectable to 80 ppm, while treated soils ranged from 1 to 2,553 ppm (see Table 7).

Table 7. Comparison of Arsenic Levels in Arsenic-treated and Uncontaminated Soils in North America

	Total arsenic content (ppm)		
Sampling site	Uncontaminated soil	Treated soil[a]	Crop
Colorada	1.3-2.3	13-69	Orchard
Flordia	8	18-28	Potato
Idaho	0-10	138-204	Orchard
Indiana	2-4	56-250	Orchard
Maine	9	10-40	Blueberry
Maryland	19-41	21-238	Orchard
New Jersey	10	92-270	Orchard
New York	3-12	90-625	Orchard
North Carolina	4	1-5	Tobacco
Nova Scotia	0-7.9	10-124	Orchard
Ontario	1.1-8.6	10-121	Orchard
Oregon	2.9-14	17-439	Orchard
	3-32	4-103	Orchard
Washington	6-13	106-830	Orchard
	8-80	106-2553	Orchard
	4-13	48	Orchard
Wisconsin	2.2	26	Potato

[a] These are results from soils that had been repeatedly treated with an arsenic pesticide or defoliant. Soils treated experimentally are not included. Data from Walsh and Keeney (1975).

Greaves (1934) studied soils from 50 orchards and found that levels of arsenic varied from 26.4 to 1,353.3 kg/ha-m (7.2 to 367.2 pounds/acre-ft). Bishop and Chisholm (1962) compared surface soil from 25 orchards to soil from control (untreated) soils and found arsenic accumulation due to the use of pesticides. In Canada, Miles (1968) studied soil from four apple orchards. The arsenic level ranged from 10.2 to 107 ppm between the trees, and from 15.6 to 121 ppm under trees. Soil from untreated vegetable fields generally had under 10 ppm of arsenic.

Arsenic from smelter emissions can contaminate the surrounding soil. Crecelius et al. (1974) reported surface soil contamination of up to 380 ppm within a 16-mile distance from a smelter stack, with suspected contamination as far as 112 miles away. Ratsch (1974) reported arsenic concentrations of 7.3 to 457 ppm within a 6-mile radius of a copper smelter.

Soil adsorption of arsenicals is dependent on soil pH, texture, iron and aluminum oxide content, phosphorous level, and the organic matter content (Woolson 1976). Arsenic that is adsorbed to soil or sediment is fixed as slightly soluble compounds (Woolson 1976). There is an equilibrium between the arsenic in solution and that fixed in the soil or sediment (Woolson 1976). Soluble arsenic is subject both to leaching, especially in sandy soil where there is little potential for forming adsorption complexes, and to removal by surface run-off to ground waters, lakes, and rivers.

Unlike heavy metals, there is decreased adsorption of arsenates in soils with high pH (Misra and Tiwari 1963). Depending on soil texture, soils adsorb arsenate in the following decreasing order: clay, clay loam, silt, loam, loam sand. Arsenic, like many heavy metals, is persistent in soils with a high concentration of hydrous oxides, especially those of iron and aluminum found in laterite, bauxite, and silicate soils. Arsenic is decreasingly reactive with Fe > Al > Ca > Mg, to form increasingly soluble salts (EPA 1976c). If levels of reactive Fe, Al, and exchangeable Ca are low, arsenic is more likely to leach (Woolson et al. 1971a). Because of chemical similarities, arsenate ions can compete with phosphate ions for adsorption to soil minerals. Fixed arsenate can be readily replaced in the presence of phosphate ions (Woolson 1972). Increasing calcium levels will decrease arsenate retention in soil.

Precipitation can affect the persistence of arsenic in soil. Over a period of years, arsenic will leach from soil with adequate rainfall. With limited rainfall, however, arsenic can accumulate in soils where leaching occurs more slowly due to high iron and aluminum oxide content.

Arsenic in the soil can be removed naturally by volatilization (from biotransformation), leaching, windborn dust, run-off, plant uptake, and crop removal.

(b) Water

Small quantities of arsenic occur in virtually all natural waters. Ground waters usually contain more arsenic than surface waters. Naturally occurring arsenic in sea water averages 0.003 ppm while rivers average about 0.0004 ppm (Bowen 1966). Elevated arsenic levels in water are usually the result of pollution. The average content of arsenic in fresh water (about 1.5 to 2 ug/liter) is below the recommended drinking water standards for the United States (Woolson 1975). Water near natural deposits of arsenic or areas of volcanic activity tend to have higher levels of arsenic.

Although there is disagreement among scientists as to the oxidation state of arsenic in sea water, it is agreed that there is an equilibrium between arsenate and arsenite forms (Woolson 1975). There are indications that, in the oxidizing layers of the ocean, arsenic is in the pentavalent state, while at lower depths it is reduced to the trivalent state (Woolson 1975). This equilibrium may also exist in stratified lakes.

The strong association of arsenic with clays high in iron and aluminum oxides is an important means of transferring arsenic to streams, lakes, and sediments [see Section I.F.(1)(a)]. Arsenic can enter natural waters by run-off and leaching from arsenic-treated soils. The hydrous metal oxides in the sediments can adsorb the arsenic, removing it from solution, thereby preventing build-up of high concentrations (Woolson 1976). Sediments in polluted rivers have been found to contain up to 220 ppm of arsenic (Oak Ridge 1976).

Arsenic can be removed from solution by volatilization (as alkyl arsines), adsorption by clays and detritus, and coprecipitation with metal ions (Ferguson and Gavis 1972).

(c) Air

Arsenic in the atmosphere is primarily the result of human activities and, to a lesser extent, volcanic and bacterial action. There is generally low atmospheric arsenic except near local pollution sources such as metal smelters, cotton gins, and areas of pesticide application. The air of most U.S. cities contains a small amount of arsenic, while air in rural areas has a relatively low concentration of arsenic (Sullivan 1969).

Arsenic moves in air adsorbed to particulate matter, and it is returned to the soil by direct fallout or by precipitation (Woolson 1976). It has been hypothesized that volatile arsenicals released to the atmosphere are oxidized in the presence of light and returned to the soil via dry fall (as particulate matter) or in precipitation (Woolson and Kearney 1973).

(2) Degradation and Transformation

In nature, most arsenicals are converted to arsenate (pentavalent) which is the stable oxidation state in oxygenated environments. Arsenite (trivalent) is the dominant form in anaerobic conditions (i.e., flooded soils, submerged sediment layers). Arsenate may be reduced to arsenite under conditions of low pH (Misra and Tiwari 1963). Arsenite will not persist for long periods in well-aerated soils with significant biological activity. Oxidation also occurs in alkaline soils or those containing ferric and aluminum oxides (Misra and Tiwari 1963).

In air, arsenic is transformed by abiotic oxidation (Lee et al. 1977). In the soil and water, transformation is usually mediated by organisms (Sandberg and Allen 1975). Trivalent forms (arsenite) can be oxidized to the pentavalent (arsenate) both abiotically and biotically. Pentavalent forms can be reduced anaerobically. Methylation occurrs anaerobically and aerobically by many microbial species (Cox 1975).

In sea water, there is an equilibrium between arsenate and arsenite with the pentavalent form predominating (Woolson 1975). In the aerobic (oxidizing) layers of the ocean, the reduced forms of arsenic will be oxidized to arsenate. At lower ocean depths where oxidation is not as great, chemical or microbial reduction may occur (Woolson 1975).

Both arsenates and arsenites can precipitate with ferric hydro-oxides in water (Woolson 1975). Ferric arsenates and arsenites can then accumulate in ocean sediments where solubilization as arsines, stabilization as sulfides, or reduction to arsenic metal can occur. Turbulence and convection can transport arsenates to lower oxygen-depleted depths where they may be reduced to arsenites or AsS_2 (Woolson 1975).

G. Residues

(1) Soil

Residual arsenic tends to be concentrated in the surface layers of the soil (Jones and Hatch 1945; Vandecaveye et al. 1936). With regular treatments of sodium arsenite, arsenic was reported to have accumulated to the extent that leaching equaled the addition of arsenite (Tammes and de Lint 1969).

EPA's National Soils Monitoring Program (Memo 1977a, 1977b) has limited data on noncropland (i.e., nonurban and nonagricultural) soil sampling for arsenic residues for fiscal year (FY) 1969 and 1972. In FY 1969, a total of 198 noncropland soil samples were analyzed from 11 states; 195 samples showed arsenic residues. In eight of the states, 100% of the sites showed arsenic residues, and in the other three 94.1, 94.7, and 97.3% of the sites showed arsenic residues. The lowest arithmetic mean for arsenic residues from any one state was 1.47 ppm, and the highest was 8.43 ppm. The lowest residue level in any one state was 0.33 ppm, and the highest was 39.07 ppm.

In FY 1972, a total of 254 noncropland soil samples were analyzed from 18 states and geographic regions; 242 samples showed arsenic residues. In 12 of the states, 100% of the sites showed arsenic residues, and in the other six 75.0 to 94.7% of the sites showed arsenic residues. The lowest arithmetic mean for arsenic residues from any one state was 1.68 ppm, and the highest was 16.66 ppm. The lowest residue level in any one state was 0.41 ppm, and the highest was 38.05 ppm.

As part of this program, soil samples were analyzed for elemental arsenic (As) in selected urban areas from 1971 through 1976, and in agricultural soil from FY 1969 through 1972. Analysis of urban samples is not yet complete for cities sampled in 1976 and for several in 1975 For the 24 cities on which analysis has been completed, however, 20 showed arsenic residues in 100% of the samples analyzed; the other four had arsenic residues in 92.3 to 98.9% of the samples analyzed. The lowest arithmetic mean for arsenic residues from any one city was 1.84 ppm, and the highest was 25.28 ppm.[3/] Agricultural soil samples were taken from

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[3/] The highest average arsenic level was in Tacoma, Washington, site of a copper smelter which, based on the high ambient arsenic levels observed, has been described as "one of the most important individual sources of arsenic with emissions of 310 tons/year" (EPA 1975b). These residues seem clearly to be of industrial, rather than agricultural, origin.

the National Soils Monitoring Program sites. Arsenic analyses were discontinued in FY 1973. Because arsenic is a naturally-occurring element in soils, arsenic was detected in about 99% of the samples, and the arithmetic mean remained fairly constant during the period of sampling.

Carey et al. (1976) studied 14 U.S. cities of various sizes for pesticide residues in soil during the summer and fall of 1970. Sample sites (231 m^2) were randomly selected in each city. Arsenic residues were found in 97% of the samples analyzed. Geometric mean values for arsenic ranged from 0.5658 ppm in Cheyenne, Wyo., to 8.5081 ppm in Philadelphia, Pa.

In 1970, Steevens et al. (1972a) studied arsenic residues in soil from Wisconsin potato fields in which sodium arsenite had been extensively used as a defoliant from 1958 to 1968. Composite soil samples of 10 randomly selected cases from the plow layer were taken from 18 potato fields in the three principal potato-growing areas of Wisconsin. The authors noted that the level of naturally occurring arsenic in soil ranged from 2 to 10 ppm. This study showed arsenic soil levels of <10 ppm at seven sites and from 10.0 to 25.7 ppm at 11 sites. The authors concluded that past usage of sodium arsenite in these fields had not resulted in arsenic levels which would be detrimental to crops.

(2) Water

A report on drinking water and health by the National Academy of Sciences (NAS 1977a) noted that the maximum no-observed-effect level for arsenic in water is <100 ug/liter. The report called the current mandatory U.S. drinking water limit of 50 ug arsenic/liter "only a meager margin of safety," since intake from 2 liters/day of water containing 20 ug arsenic/liter is slightly greater than 10% of the median total intake of arsenic. The current World Health Organization and U.S.S.R. limits for arsenic in drinking water are 50 ug/liter.

(3) Air

Arsenic residues in air result from smelting of metals; burning of coal, vegetation treated with arsenicals, and agricultural wastes; ginning of cotton; and use of arsenical pesticides.

The use of arsenical pesticides constitutes a major source of air pollution. From 1937 to 1940, Neal et al. (1941) studied the amount of arsenic and lead in the air from the use of lead arsenate in orchards. The arsenic concentration was highest when pesticide containers were burned (16,670 ug/m^3), followed by mixing the pesticide (1,850 ug/m^3), picking the fruit (880 ug/m^3), spraying the pesticide (140 ug/m^3), and thinning the fruit (80 ug/m^3).

Arsenic in dusts and gases from cotton gins is another source of arsenic air pollution. The pesticides are used for weed control and for cotton desiccants. From 46 to 91 miles downwind of a cotton gin in Texas, arsenic concentrations in the air varied from 600 to 141,000 ng/m^3 (HEW 1967).

(4) Fish

Mackenthun (1960) studied the long-term effects of sodium arsenite used as an aquatic herbicide in Wisconsin. One lake with an area of 2,501 acres had received the equivalent of 87 pounds of As_2O_3 per acre, during the period 1950 to 1960, along the shoreline. Arsenic content in fish from this and an untreated lake was determined. One largemouth bass from the treated lake showed no arsenic residues. A largemouth bass, a black crappie, and a bullhead showed <0.05 ug/g As_2O_3 in flesh and 0.1 ug/g in skin and scales. One 7-inch bluegill had 0.064 ug/g in flesh and 0.27 ug/g in flesh and 0.127 ug/g in skin and scales. Fish from the untreated lake showed no arsenic residues.

Lucas et al. (1970) conducted a study on concentrations of trace elements, including arsenic, in fishes from three Great Lakes (Michigan, Superior, and Erie) during 1968 and 1969. Species used for whole-body analyses were alewives (*Alosa pseudoharengus*), spottail shiners (*Notropis hudsonius*), and trout-perch (*Percopsis omiscomaycus*). Since alewives were small, about 20 were combined for each sample; spottail shiners and trout-perch were analyzed individually.

Alewives from Lake Michigan contained 23 ppb arsenic (based on a single determination); spottail shiners from Lake Michigan contained 3 ppb (based on a single determination); and trout-perch from Lake Michigan contained an average of 43 ± 12 ppb. Spottail shiners from Lake Erie contained 3.5 ± 3.0 ppb arsenic/g of tissue, and trout-perch from Lake Superior contained 7 ± 2 ppb. The authors noted that arsenic concentrations in trout-perch from Lake Michigan appeared to be significantly higher than in those from Lake Superior.

The authors also determined the arsenic concentration in livers of 10 species of fish. Lake herring (*Coregonus artedii*) from Lake Superior contained an average of 69 ± 30 ppb arsenic/g of tissue; lake whitefish (*C. clupeaformis*) from Lake Superior contained 6.4 ± 0.7 ppb; bloater (*C. hoyi*) from Lake Superior contained 53 ± 17 ppb; round whitefish (*Prosopium cylindraceum*) contained 5.6 ± 3.4 ppb; and lake trout (*Salvelinus namaycush*) contained 80 ± 10 ppb. Fish from Lake Erie which contained arsenic concentrations included goldfish (*Carassius auratus*), 0.3 ± 0.2 ppb; white bass (*Roccus chrysops*), 0.8 ± 0.4 ppb; and walleye (*Stizostedion v. vitreum*), 0.8 ± 0.5 ppb.

Walsh et al. (1977) conducted a study of arsenic and heavy metal residues in fish from 1971 to 1973 from 100 monitoring stations throughout the 50 states and Puerto Rico. The detection limit for arsenic was 0.05 mg/kg. The authors noted that only selected samples were analyzed in 1973 and that these figures should be used cautiously as trend data. The results showed that arsenic was present in more than 90% of the samples. Arsenic levels ranged up to 3.40 mg/kg in 1971, 1.70 mg/kg in 1972, and 1.24 mg/kg in 1973. Fish from the Great Lakes had high residues more frequently than fish from other stations.

(5) Birds

Martin and Nickerson (1973) conducted a nationwide study of arsenic and heavy metal residues in starlings (*Sturnus vulgaris*), which were collected in 1971 at 50 sites throughout the continental United States. The authors noted that arsenic residues were low (<0.04 ppm). Only one sample from Michigan showed a higher arsenic content (0.21 ppm). Eight samples showed no detectable arsenic resiudes.

White et al. (1977) conducted a similar study in starlings, which were collected in 1973 at 51 sites throughout the continental United States. The authors noted that residue levels were generally low; arsenic residues ranged from <0.05 to 1.40 ppm. The average level for all 51 sites was 0.160 ppm. The authors also stated that there had been a significant increase in arsenic residues in starlings since 1971. Arsenic residues were 88% higher in 1973. Twenty-eight of 1973 samples (55%) contained residues of 0.10 ppm or greater.

Blus et al. (1977) studied residues of organochlorine pesticides and 10 heavy metals in livers and eggs of brown pelicans (*Pelecanus occidentalis*), a rare and endangered species, from 1969 through 1973. Pelican colonies in Florida (1969 to 1970) and South Carolina (1971 to 1972) were sampled. Arsenic residues in eggs from South Carolina were three times higher than those from Florida. Arsenic residues in eggs from South Carolina and Florida, respectively, ranged from 0.076 to 0.85 ug/g and 0.07 to 0.18 ug/g fresh wet weight.

Livers of four brown pelicans, shot in 1970, were checked for arsenic residues. Livers of an adult female and an immature male, both shot in Florida, contained 0.63 and 0.89 ug of arsenic/g fresh wet weight, respectively. Livers of a 6-week-old female and an adult male, both shot in South Carolina, contained 0.36 and 0.29 ug/g, respectively.

Livers of four brown pelicans, found dead in 1972 and 1973, were also checked for arsenic residues, with the following results: 0.47 ug arsenic/g fresh wet weight in an adult female found in Florida in 1972; 0.23 ug/g in an adult female found in Georgia in 1972; 0.54 in an immature male found in Florida in 1973; and 1.02 ug/g in an 8-week-old female found in South Carolina in 1973.

The authors noted that each egg and tissue sample of brown pelicans that was analyzed contained residues of ten heavy metals, but that the significance of these residues to the pelicans was undetermined.

Lynch (1973) studied the occurrence of selected toxic metals, including arsenic, in pheasants (*Phasianus colchicus*) in Ohio. Twenty-six samples of pheasant breast muscle were analyzed for arsenic with a detection limit of 0.001 ppm. Sixteen samples contained detectable arsenic residues. The highest amount found was 0.172 ppm. The author indicated that, although lead arsenate was recommended for use in apple orchards in 1973, only 1% of Ohio orchards were treated with it. The author did not state whether arsenic residues in pheasants resulted from natural background levels or from agricultural or industrial pollution.

(b) Mammalian Wildlife

Lynch (1973) studied the occurrence of selected toxic metals in cottontail rabbits (*Sylvilagus floridanus*), squirrels (*Scuirus carolinensis* and *S. niger*), and white-tailed deer (*Odocoileus virginianus*) in Ohio. The detection limit for arsenic residues was 0.001 ppm. Eleven samples of deer leg muscles were analyzed; six contained detectable arsenic residues. The highest amount found was 0.217 ppm.

Three samples of rabbit femur were analyzed, but none contained detectable arsenic residues. Twenty-two samples of rabbit leg muscle were also anlyzed; four contained detectable arsenic residues. The highest amount found was 0.020 ppm. A single sample of squirrel brain contained 0.055 ppm arsenic. Of four samples of squirrel femur analyzed, one contained arsenic at 0.017 ppm. A single sample of squirrel liver contained 0.035 ppm arsenic. Twenty-three samples of squirrel leg muscle were analyzed; 13 contained detectable arsenic residues. The highest amount found was 0.035 ppm.

(7) Food and Feed

The following studies indicate that inorganic arsenic residues (as As_2O_3) in various foods are generally below the established tolerance levels. Arsenic occurs in food and feed as either a natural constituent or as a residue from pesticides or smelter pollution.

Generally, the only foods which are high in arsenic are seafoods. Schroeder and Balassa (1966) sampled food and

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beverages available in grocery stores and found that fish and other seafoods had the highest levels (mean of 4.64 ppm) while fruits had the lowest content (mean of 0.042 ppm).

Chapman (1926) reported mean values of up to 80 ppm of arsenic in mussels, oysters, and scallops, while mixed fresh water fish contained 0.65 ppm.

Bradicich et al. (1969) studied arsenic residues in samples of various food commodities in Texas in 1963 from areas where arsenical defoliation had been practiced. The study was continued in 1964, 1965, and 1966 for cottonseed products. A majority of the samples for 1963 (77 out of 107) showed arsenic residues; the average residue levels ranged from 0.01 to 0.90 ppm, and the maximum residue levels ranged from 0.01 to 3.72 ppm. Over 95% of the cottonseed oil and cottonseed meal samples showed residues significantly higher than the other commodities.

Of the 159 cottonseed-product samples tested from 1963 through 1966, 143 were positive, but only three were above the established tolerance level of 4 ppm for As_2O_3 (see Section I.D). The average residue level for all hull samples was 1.2 ppm, for all meal samples 1.4 ppm, and for oil samples (the main product of human consumption) 0.4 ppm.

In 1970 Steevens et al. (1972a) studied arsenic levels in flesh and peelings of potato tubers grown in Wisconsin potato fields on which sodium arsenite had been extensively used as a defoliant from 1958 to 1968. (The use of sodium arsenite as a potato vine defoliant was cancelled in 1969.) The arsenic concentration in potato peelings ranged from 0.2 to 2.3 ppm and in potato flesh ranged from a trace to 0.6 ppm. The arsenic (As) tolerance limit at that time was 2.6 ppm.

Crecelius (1977a) analyzed 19 samples (plus one duplicate of each of two samples) of domestic table wines from several types of arsenic (arsenite, arsenate, methylarsonic acid [MAA], and dimethylarsinic acid [DMAA]). Arsenite concentration in these samples ranged from < 1 to 420 ppb, and arsenate from < 1 to 110 ppb. Both MAA and DMAA levels were below the detection limit of 1 ppb in these samples. The United States does not have an arsenic standard for wine, although a maximum value of 20 ppb was once recommended. Great Britain's maximum tolerable arsenic level in wine is 100 ppb, and several other countries (not identified by the author) have a limit of 200 ppb. The maximum arsenic level for drinking water in the United States is 50 ppb. The proposed 20 ppb U.S. Standard for wine was exceeded by 15 of the 19 samples for arsenite and 14 samples for arsenate; the 50 ppb U.S. water standard was exceeded by 12 samples for arsenite and two samples for arsenate; the 100 ppb British

Standard for wine was exceeded by ten samples for arsenite and one sample for arsenate; the 200 ppb standard from "other countries" for wine was exceeded by five samples for arsenite. The author did not investigate agricultural practices in the vineyards. The author described the arsenic levels in some samples as "surprisingly high" and suggested they were due to use of arsenicals in the production of grapes. The tolerance level for lead arsenate on grapes is 7 ppm and for sodium arsenate is 3.5 ppm. There is an interim tolerance of 0.5 ppm for use of sodium arsenite on grapes.

The Food and Drug Administration (FDA) conducts periodic Market Basket Surveys of pesticide residues in total diet samples of ready-to-eat food. The samples are representative of a two-week intake for males 16 to 19 years old from moderate income families. Composite samples of food commodity groups are analyzed for arsenic as As_2O_3. The analytical method does not distinguish between naturally occurring arsenic and arsenic residues from industrial or agricultural sources. The following studies reported on arsenic residues found in FDA's Market Basket Survey.

Cummings (1966) reported that arsenic residues in samples from Baltimore, Maryland, analyzed in May 1964, ranged from 0.10 to 4.7 ppm. Food commodity groups in which arsenic residues were found were meat, fish, and poultry; grain and cereal products; potatoes; legume vegetables; root vegetables; and fruit.

Duggan et al. (1966) reported on pesticide residues in diet samples collected bimonthly from June 1964 through April 1965 from retail food stores in Boston, Massachusetts; Kansas City, Missouri; and Los Angeles, California. Arsenic (As_2O_3) was found in six of the 216 composite samples assayed, at levels ranging from 0.1 to 4.7 ppm. Arsenic was present in one of the 18 meat, fish, and poultry samples at 0.12 ppm; in one of the 18 grain and cereal samples at 0.10 ppm; in one of the 18 potato samples at 4.7 ppm; in one of the 18 legume vegetable samples at 0.11 ppm; in one of the 18 root vegetable samples at 0.10 ppm; and in one of the 18 fruit samples at 0.18 ppm.

Duggan and Weatherwax (1967) reported on the average daily intake of all pesticide residues in or on the total diet samples collected in 25 cities from June 1964 through April 1966. The results showed that the daily intake of arsenic residues (As_2O_3), expressed in milligrams per day, for samples collected from June 1964 through April 1965, were trace (>0.001 mg) for meat, fish, and poultry samples; 0.002 for grains and cereals; 0.063 for potatoes; 0.001 for legume vegetables; 0.001 for root vegetables; and 0.002 for fruits.

Results for samples collected from June 1965 through April 1966 were 0.003 for meat, fish, and poultry; 0.001 for grain and cereals; trace for root vegetables; 0.001 for garden fruits; and 0.001 for sugars and adjuncts. The authors noted that whereas the average 16-to-19-year-old male consumes about 8.8 pounds of food and drink daily, the average individual in the general population consumes only about 4.8 pounds daily.

Duggan et al. (1967) reported on pesticide residues in total diet samples collected from June 1965 through April 1966. Arsenic residues, ranging from 0.1 to 0.5 ppm (As_2O_3), were found in 5 of 28 composites of meat, fish, and poultry; in one of 28 composites of grain and cereals at 0.1 ppm; in one of 28 composites of root vegetables at 0.1 ppm; in one composite of garden fruits at 0.1 ppm; and in one of 28 composites of sugars and adjuncts at 0.1 ppm.

Martin and Duggan (1968) reported on 360 total diet samples, from 30 markets in 29 cities for June 1966 through April 1967. Arsenic (As_2O_3) was found in 33 diet samples; residue levels ranged from 0.1 to 0.4 ppm. Eight samples showed arsenic residues below the analytical sensitivity level.

H. Pesticide Episode Reports System (PERS)

EPA's Pesticide Program maintains a Pesticide Episode Reports System (PERS) which collects reports of pesticide exposure affecting humans, domestic animals, livestock, and wildlife (EPA 1977). According to those records, there were 308 episodes from 1966 through April 1977 involving various inorganic arsenicals.

There were 25 episodes involving use of arsenic trioxide alone as a rodenticide or insecticide. All of these involved humans. For 15 of these 25 episodes, which include seven fatalities, there was substantial evidence that arsenic trioxide was directly involved; and for eight episodes, there was insufficient evidence to either prove or disprove involvement of arsenic trioxide.

There were 17 episodes involving use of arsenic trioxide as an herbicide. Seven of these involved other active ingredients, including arsenic acid, lead arsenate, arsenous oxide, heptachlor, and sodium chlorate. Six of these 17 episodes involved livestock, five involved crop contamination, three involved humans, and one each involved a bee kill and water contamination. For seven of these episodes which include one fatality, there was substantial evidence that arsenic trioxide was directly involved; for five episodes, there was insufficient evidence; and for one episode, there was evidence which proved that arsenic trioxide was not responsible.

There were 128 episodes involving use of sodium arsenate and/or arsenite as an insecticide and wood preservative. One of these episodes involved other active ingredients. One of these episodes involved a dog, one involved livestock, and the other 126 episodes involved humans, mostly children. For 14 of these 128 episodes which include two fatalities, there was substantial evidence that sodium arsenate/arsenite was directly involved; for 16 episodes which include one fatality, there was circumstantial evidence; and for 98 episodes which include one fatality, there was insufficient evidence to either prove or disprove involvement of sodium arsenate/arsenite.

There were 50 episodes involving use of sodium arsenite as an herbicide. In three of these episodes other forms of arsenic were also involved. One each of the 49 episodes involved a stand of trees and a dog; 20 involved livestock; and 28 involved humans. For 34 of these episodes which include twenty fatalities, there was substantial evidence that sodium arsenite was directly involved; for five episodes, there was circumstantial evidence; for 10 episodes which include one fatality, there was insufficient evidence; and for one episode, there was evidence which proved that sodium arsenite was not responsible.

There were 33 episodes involving use of lead arsenate as an insecticide. Boric acid was involved in two of these episodes, of which 31 involved humans, one involved livestock, and one involved contamination of well water. For five of these 33 episodes, there was substantial evidence that lead arsenate was directly involved; and for 28 episodes, there was insufficient evidence to either prove or disprove involvement of lead arsenate. There were no fatalities in any of the episodes involving humans.

There were 16 episodes involving use of calcium arsenate as an insecticide or herbicide. Five of these involved calcium arsenate alone, and eleven also involved other active ingredients (mostly metaldehyde). Twelve of these episodes involved humans, two involved livestock, and one each involved a dog and well water contamination. For three of these 13 episodes, there was substantial evidence that calcium arsenate was directly involved; for four episodes, there was circumstantial evidence; for eight episodes which include one fatality, there was evidence which proved that calcium arsenate was not responsible.

There were three episodes involving use of copper acetoarsenite as an insecticide, all of which involved humans.[4] For one episode, there was substantial evidence that copper acetoarsenite was directly involved; and for two episodes, there was insufficient evidence to either prove or disprove involvement of copper acetoarsenite. No fatalities were reported.

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[4] In one episode, other active ingredients (MSMA, diazinon, and malathion) were also involved.

In addition, 36 episodes involving various inorganic arsenicals were reported which were not use-related. These episodes involved suicides and homicides, fires, and transportation accidents.

I. Lead Arsenate - Chronic Effects Due to Lead

Although lead arsenate contains a lead moiety, the chronic effects seen in vintners and others who use the compound do not correspond to chronic lead effects. Rather the effects are typical of those seen with other inorganic arsenicals (see Section IV. B). In the human body, inorganic lead has damaging effects on the hematological, neurological, and renal systems (Nordberg 1976). The Agency will conduct a separate evaluation of possible adverse effects due to lead in the future.

Lead interrupts many steps in the pathway of heme synthesis and formation of hemaglobin, both part of the blood-forming process. Lead also shortens the life span of erythrocytes. Lead affects both the central and peripheral nervous systems. Encephalopathy is a major effect on the central nervous system and usually results from a more intensive and prolonged exposure to lead than that inducing hematological effects. The acute form may be fatal. Peripheral nervous system disorders due to chronic lead exposure are characterized by selective involvement of motor neurons with little sensory involvement. Lead effects on the renal system, such as nephritis, are seen primarily in adults with heavy occupational exposure. The long-term effect on the kidneys is nonspecific nephropathy.

Teratogenic and reproductive effects of lead in humans have not been studied extensively. There are reports of steriltiy, stillbirths, and miscarriages in women industrially exposed.

J. Arsenate and Arsenite: Interconversion

Studies discussed in this portion of the position document indicate arsenate (in either the organic or inorganic form) to be the predominant form of arsenic in mammals. When inorganic arsenite is administered the majority of the arsenic is converted (oxidized) to the less acutely toxic pentavalent form. Information on the conversion of the less acutely toxic pentavalent arsenicals (arsenates) to the more acutely toxic trivalent form (arsenites) is of importance in evaluating the environmental and health effects of the inorganic arsenic compounds used as pesticides.

Based on studies presented in this section and on an analysis by EPA's Carcinogen Assessment Group (EPA 1978) the Agency concludes that although oxidation of trivalent arsenic (arsenite) to the pentavalent form (arsenate) is the favored reaction, pentavalent arsenic (arsenate) can be reduced *in vivo* to the trivalent form (arsenite). This conclusion is supported by: 1) *in vivo* experiments in mammals, 2) qualitative similarities in toxic effects of arsenite and arsenate, and 3) data showing an equilibrium ratio between arsenate and arsenite. For additional information dealing with metabolism see Sections I.E(1)(c), (d), and I.E.(5).

(1) Metabolism - In Vivo Interconversion

The following studies show that inorganic arsenite (trivalent) is oxidized *in vivo* to arsenate (pentavalent) and/or that inorganic arsenate is reduced *in vivo* to arsenite.

Mealey et al. (1959) demonstrated that conversion takes place within human body tissues. Radioactive inorganic arsenite was administered intravenously to five humans; the amounts of arsenite and arsenate in the urine were monitored over time. During the first four days, the percentage of arsenite to arsenate in the urine leveled off at about 75% arsenate. Results indicated that oxidation of arsenite to arsenate took place within body tissues.

Winkler (1962) had findings similar to Mealey et al. (1959) after identifying and estimating arsenic residues in livers of rats ingesting arsenicals. Rats were fed sodium arsenite and sodium arsenate at 125 and 250 ppm of arsenic. The animals were killed after 90 days, and their livers were analyzed. The results showed that trivalent inorganic arsenic was largely changed to the pentavalent form in the rat. Pentavalent arsenic, however, was not reduced to the trivalent form.

Lakso and Peoples (1975) observed essentially similar levels of methylated arsenic and inorganic arsenic (individual species not measured) after feeding experiments with cows and dogs in which both sodium arsenate and potassium arsenite were administered. The authors suggested that the short delay in increased methylated arsenic excretion after arsenite feeding is indicative of the oxidation of arsenite to arsenate prior to methylation.

Crecelius (1977b) studied changes in the chemical speciation of arsenic following ingestion by man. The subject of this study was one 30-year-old male whose diet was controlled to minimize the intake of arsenic from any other food or drink before and during the experiment.

In the experiment, 450 ml of wine, containing 50 ug trivalent and 13 ug pentavalent arsenic, was ingested. The major form of arsenic excreted in the urine after 61 hours was dimethylarsinic acid (DMAA), a pentavalent arsenical, which accounted for about 50% of the total 63 ug of arsenic ingested. Trivalent and pentavalent arsenic each accounted for 8%, and methylarsonic acid (MAA), another pentavalent arsenical, for 14%. The author concluded that, when trivalent arsenic is ingested, a small portion is excreted unchanged as arsenite, but that the majority is oxidized and methylated in the body and excreted as DMAA and MAA (pentavalent arsenic).

Conversion of the trivalent to the pentavalent form of arsenic has often been described in the literature (Oak Ridge 1976; EPA 1976b; AWPI 1977).

Although the *in vivo* oxidation of trivalent arsenic to pentavalent arsenic is the favored reaction, the possibility of reduction *in vivo* of pentavalent arsenic to the trivalent form has been suggested by several investigations.

Thuret (1939) reported that *in vitro* experiments showed reduction of pentavalent arsenic, in contact with liver pulp, to the trivalent form after six hours. Lanz et al. (1950), in a study on rats using radio-labeled sodium arsenate, reported that 10 to 15% of the inorganic arsenic recovered from the urine was in the trivalent form.

Ginsburg and Lotspeich (1963) and Ginsburg (1965) observed that arsenates are reduced to arsenites under certain conditions. These studies are of particular concern to the Agency in that they report reduction _in vivo_.

Ginsburg and Lotspeich (1963), in a study on the interrelation of arsenate and phosphate transport in the dog kidney, reported _in vivo_ reduction of arsenate to arsenite during intravenous infusion of a solution containing pentavalent arsenic and 1.5% trivalent arsenic. About 5.5% of the plasma arsenic and 14% of the urinary arsenic was in the trivalent state during the first three periods of the experiment. The authors also noted a net secretion of trivalent arsenic in the urine because of intracellular reduction by renal tissue.

In further investigations, Ginsburg (1965) demonstrated that some infused arsenate is reabsorbed by the dog kidney and reduced to arsenite. A representative experiment measured the kidney clearance of arsenate and arsenite during the intravenous infusion of a solution containing arsenate (98.6%) and only 1.4% arsenite. If both valence forms are treated similarly by the kidney (i.e., no conversion), the relative proportions of pentavalent and trivalent arsenic in the urine should be the same as in the plasma. After 35 minutes of infusion, however, 5.6% of the plasma arsenic and 14% of the urine arsenic was trivalent. Based on comparisons with *in vitro* experiments, this higher level of arsenite *in vivo* was not accounted for by simple filtration by the kidney or by a greater reduction of arsenate in the urine than in the plasma. In 15 control experiments the ratio of the percent of arsenite in urine to the percent of arsenite in plasma ranged from 1.9 to 4.2 (mean 2.8). After infusion of arsenate, there was a net renal tubular reabsorption of arsenate (26% of the filtered arsenate) and a net secretion of arsenite occurred. The rate of arsenite secretion was directly proportional to the rate of arsenate reabsorption. There was also a greater concentration of arsenite in renal venous plasma than in renal arterial plasma.

In another experiment where a solution of arsenite (91.6%) containing 8.4% arsenate was infused into the dog, arsenate appeared in the plasma and urine at levels greater than 8.4%, indicating *in vivo* oxidation. There was a net reabsorption of trivalent and, to a lesser extent, of pentavalent arsenic. There was no net secretion into the urine of arsenite during this infusion which indicates that arsenite is probably not actively transported in the kidney. When arsenate was then added to the infusion solution in the second phase of the experiment, the additional arsenate was available for reabsorption. Consequently, the former net reabsorption of arsenite changed to a net secretion of arsenite, indicating a conversion of arsenate to arsenite.

After experimentally examining several hypothetical explanations for the increased presence of arsenite in the urine and plasma, the author concluded that arsenite is secreted into urine and blood from an intracellular site (tubular cells) in the kidney, where some of the arsenate reabsorbed from the glomerular filtrate is intracellularly reduced to arsenite. This process is dependent on a concentration gradient for arsenite from cell to urine which is established by the intracellular reduction of the arsenate reabsorbed from the glomerular filtrate. Ginsburg noted that this gradient for arsenite from cell to urine and blood was established only when the arsenic infusion contained large amounts of arsenate relative to arsenite. He also noted that it is not known whether the arsenic retained in the kidney cells is in the form of arsenate or arsenite.

Peoples (1964), however, failed to show _in vivo_ reduction of arsenate to arsenite. In this study arsenic acid (a pentavalent arsenical) was fed to lactating Holstein cows at levels of 0 to 1.25 mg/kg daily for eight weeks. The results showed no significant variation in weekly milk samples at any feeding level from controls, although small amounts of arsenic acid were detected. The arsenic found in the livers of two cows fed arsenic acid was entirely in the pentavalent state. The author concluded that the small amounts of tissue-bound arsenic were entirely in the pentavalent form and that there was no evidence that it was partly reduced to the trivalent form.

The Occupational Safety and Health Administration [OSHA (1978)], has concluded "that the presently available evidence indicates that there is little or no conversion of pentavalent to trivalent arsenic in the body." In reaching this conclusion OSHA relied heavily on testimony by Dr. Peoples (1975) during hearings held by OSHA on inorganic arsenic. Dr. Peoples concluded that the Ginsburg findings "could not be relied on because the analytical method was not accurate in the range of the reported sample size."

In an effort to answer the question of the realiability of the studies by Ginsburg and Lotspeich (1963) and Ginsburg (1965), EPA submitted these studies for outside review. In validation reports for the Agency on both Ginsburg papers, Lombardini (1978b; 1978c) concludes that Ginsburg's observation of *in vivo* reduction of arsenate to arsenite were supported by the data given. In addition, Lombardini (1978a) evaluated the paper by Crawford and Storey (1944) which described the analytical method used by Ginsburg. Lombardini stated that the method was "somewhat of a classical technique...still in use in 1978." He added, "This procedure has been time-tested and is valid."

Although the issue is not free from doubt, the Agency concludes that sufficient scientific information is available to support the conclusion that pentavalent arsenic can be converted to trivalent arsenic in the body. In questions such as this one on the frontiers of scientific knowledge, decision-making must to a large extent rest on policy judgments. In view of the scientific information available and the serious health issues at stake, the Agency has made the judgment that it is in the public interest to bring forward through the RPAR process its tentative conclusion that pentavalent arsenic converts to trivalent arsenic *in vivo*. The RPAR process is intended to be an information-gathering process which will provide the broadest base possible for final regulatory decision-making.

(2) Toxicity - Qualitative Similarities and Quantitative Differences

The similarity of the toxic effects of trivalent and pentavalent arsenicals may provide additional support for the proposition that there is *in vivo* interconversion of arsenate to arsenite. The following studies describe some of the qualitative similarities and the quantitative differences in the effects of arsenate and arsenite.

The acute toxicity (via intraperitioneal injections) of sodium arsenite to rats is about 3.6 times that of sodium arsenate (Franke and Moxon 1936).

In a teratology study of random-bred albino Swiss-Webster mice, Hood (1972) administered sodium arsenite via single intraperitoneal injections on days 7 to 12 of gestation at dose levels of 10 and 12 mg/kg. He observed the same spectrum of abnormalities which he had seen with a 4.5 times higher sodium arsenate treatment of 45 mg/kg (Hood and Bishop 1972). The incidence of defects was slightly higher with the 45 mg/kg arsenate. Although the author admits that the similarity of abnormalities does not prove the mechanism of action is identical for the two forms of arsenic, he does state that the experiment tends to support the theory that there is interconversion of arsenate to arsenite, which is the more acutely toxic form.

A 2-year feeding study was performed by Byron et al. (1967) on Osborne-Mendel rats and beagle dogs using sodium arsenite and sodium arsenate. For the rat experiment, the sodium arsenite dose levels ranged from 0 to

250 ppm; and for sodium arsenate they ranged from 0 to 400 ppm. The most significant effect from treatment with each arsenical was a marked enlargement of the common bile duct, which was accompanied by a 10-fold thickening of the endothelium. Both agents produced the same effect; the incidence and severity of the enlargement was slightly higher in the highest two arsenate dose groups than the highest two arsenite groups. Dogs treated with arsenate or arsenite experienced weight loss and high mortality, but displayed no histological features remarkably different from controls. The degree of mortality and weight loss was equivalent in the highest and second highest dose groups. In rats and dogs, both forms of arsenic produced the same qualitative toxic effects; the trivalent arsenite was about twice as potent as the pentavalent arsenate.

Savchuck et al. (1960) investigated the differential toxicity (expressed as growth inhibition) of arsenite and arsenate in cultured HeLa cells. Both arsenate and arsenite were found to inhibit the growth of cultured human liver cells. The levels of arsenic necessary to inhibit growth by 50% were 2.0 ppm of sodium arsenate (pentavalent arsenic) and 0.13 ppm of sodium arsenite (trivalent arsenic). Arsenite, therefore, is approximately 15 times more toxic than arsenate in this *in vitro* system. Growth inhibition is a definable toxicological end point as is acute toxicity, teratogenicity, and weight loss. Therefore, this study is of value in evaluating similarity of toxic effects.

The studies discussed above demonstrate that both forms of arsenic produce the same qualitative toxic effects, and that the trivalent arsenite is about twice as potent as the pentavalent species. These studies lend support to findings primarily by Ginsburg (1965) and Ginsburg and Lotspeich (1963) that pentavalent arsenic is converted to the trivalent form *in vivo*.

(3) *Equilibrium*

Under anaerobic conditions, there is *in vitro* evidence of an equilbrium between arsenate and arsenite that favors arsenite. The following study by Crecelius (1977a), using wine fermentation (anaerobic process) indicates a four-to-one ratio of arsenite to arsenate regardless of whether arsenite or arsenate were added to a grape juice/yeast mixture. This study demonstrates that living systems (i.e., yeast) do not affect the valence state of arsenic in an indiscriminant manner. Under a given set of physical and biological conditions the relative proportion of arsenite and arsenate will reach an equilibrium ratio. The arsenic is never all in the form of arsenate nor all in the form of arsenite. If an equilibrium between arsenate and arsenite is attained under anaerobic conditions (i.e., fermentation), it would be logical to assume that under aerobic conditions (the predominant condition in mammals) an equilibrium ratio would also exist. The concept of an equilibrium between arsenate and arsenite suggests that a certain amount of arsenite will be formed whenever a living system is exposed to arsenate. The studies by Ginsburg lend support to this theory.

Crecelius (1977a) studied the metabolic interconversion of inorganic arsenite and arsenate by yeast in the fermentation of grape juice [see Section I.G.(9)]. Trivalent arsenic (arsenite), pentavalent arsenic (arsenate), MAA, and DMAA were added to four equal samples of concord grape juice with wine yeast. The amounts of the four kinds of arsenic were determined after two weeks when the fermentation had stopped. The results showed that the fermentation process reduced approximately 60% of the initial pentavalent arsenic

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to the trivalent form, but did not methylate the trivalent arsenic and did not demethylate the MAA. The author also found that, of the arsenic in the final solutions, the final ratio of arsenite to arsenate concentration was about four to one. These results indicate that pentavalent or trivalent arsenic is changed in the fermentation process to yield the same equilibrium ratio, a 4 to 1 ratio of arsenite to arsenate (EPA 1978), regardless of the starting material. Creceluis also found in a survey of 19 domestic table wines, that the arsenite to arsenate ratio averaged about four to one.

It is likely that arsenate will be favored in aerobic conditions that might exist in intact animals. Arsenite will be favored in anaerobic systems such as wine fermentation. Ferguson and Gavis (1972) have suggested that oxidation and reduction may occur in aerobic and anaerobic natural waters, respectively.

II. REGULATORY HISTORY

Inorganic arsenicals have been the subject of numerous Federal regulatory actions since they were originally registered as pesticides. These actions have been initiated by both the U.S. Department of Agriculture and EPA.

Pesticide Registration (PR) Notice 67-2 issued on August 1, 1967, called attention to "numerous accidents involving children and domestic animals" caused by products containing sodium arsenite and arsenic trioxide. Such products labeled for home use were required to contain no more than 2.0% sodium arsenite nor more than 1.5% arsenic trioxide. In addition, labels of commercial products containing these two compounds were required to warn against storage in or around the home and against allowing domestic animals to graze on treated areas (USDA 1967).

PR Notice 68-3 issued January 10, 1968, classified use of calcium arsenate on droppings under caged layers in poultry houses as a non-food use, and allowed its registration for this use to continue in the absence of finite tolerances (USDA 1968a).

PR Notice 68-8 issued April 24, 1968, classified use of calcium arsenate on tree fruits and use of paris green as a special mosquito larvicide as non-food uses, and allowed registrations for these uses to continue in the absence of finite tolerances (USDA 1968b).

PR Notice 68-19 issued November 29, 1968, required labeling statements for certain economic poisons to protect honeybees and other pollinating insects (USDA 1968c). Arsenical pesticides were listed as "highly toxic" to bees, and labels of such products intended for foliage treatment on agricultural crops, mosquito abatement treatments, and foliage treatment on forest or shade trees were required to bear the warning, "This product is highly toxic to bees exposed to direct treatment or residue on crops."

PR Notice 71-7 issued May 7, 1971, announced that EPA was undertaking an active internal review of arsenicals and other pesticides to determine if any of the presently registered products presented questions of safety substantial enough to initiate the administrative process of cancellation (EPA 1971a).

A series of PR Notices (USDA 1968d; 1968e; 1968f; 1969a; 1969b; 1969c; and 1970a; and EPA 1971b) were issued over several years, extending certain "no residue" and "zero tolerance" registrations of various inorganic arsenicals, based on pending petitions for finite tolerances. Such extensions were granted for use of sodium arsenite on grapes, potatoes, aquatic weeds, beef cattle, goats, and sheep; and for use of lead arsenate on almonds, cabbage, lettuce, potatoes, spinach, turnips, and walnuts.

Another series of PR Notices (USDA 1968g; 1969d; and 1970b; and EPA 1972) were issued to cancel registrations of certain inorganic arsenicals for use on food in the absence of finite tolerances or exemptions. Such cancellations were issued for the use of arsenic trioxide, calcium arsenate, lead arsenate, copper acetoarsenite, sodium arsenate, and sodium arsenite on livestock and numerous food and feed crops.

III. EXPOSURE ANALYSIS

In subsequent portions of this document the Working Group will discuss the potential adverse effects of inorganic arsenicals. The Agency's decision whether to permit the registration or continued registration of these pesticides will be based, to a large extent, upon anticipated human exposure resulting from their use.

This preliminary exposure analysis discusses representative exposure situations as a basis for comment by interested parties. Before the Agency makes any regulatory decision concerning inorganic arsenical pesticides, a complete risk and benefit analysis will be performed, and the benefits of use of these pesticides will be weighed against their potential risks.

The Working Group emphasizes that a safe level for carcinogenic or mutagenic substances has never been established. Therefore, any level of a carcinogenic or mutagenic substance may cause an adverse effect and the Agency does not consider exposure when determining whether to issue an RPAR based on carcinogenic or mutagenic effects. Exposure is considered, however, when determining whether or not to issue an RPAR based on other chronic effects such as teratogenicity (birth defects). This analysis will address estimated exposure from arsenical pesticides to applicators and the general public.

Arsenical pesticides differ from synthetic organic pesticides in that arsenic is a natural element and does not degrade to less toxic constituents; therefore, the arsenic added to the environment through pesticide application will either remain as residues in the soil where applied, or be removed from the site by plant uptake, erosion, or volatilization. Since arsenic undergoes biological and chemical transformations, the arsenic from pesticides becomes indistinguishable from that occurring naturally.

The Working Group will examine representative exposure situations for each inorganic arsenic compound (see Table 8).

Table 8. Representative Exposure Situations

Agricultural Exposure (including Home and Garden)

1. Applicator exposure resulting from the use of arsenical pesticides on food crops, weeds, etc.; and
2. Exposure resulting from the consumption of food or feed crops treated with arsenical pesticides;

Exposure Resulting From the Treatment of Wood With Arsenical Wood Preservatives and Subsequent Use of Treated Wood

1. Large-scale industrial situations;
2. Intermittent application to wood during on site construction;
3. Exposure from the handling, sawing, and use of treated wood products; and
4. Exposure to individuals living or working in dwellings containing arsenic-treated wood.

When there is the potential for teratogenic effects, the Working Group must determine whether an ample margin of safety exists between the level of arsenic which produces teratogenic effects and the level to which humans can reasonably be anticipated to be exposed. Teratogenic effects occur only when the woman is exposed to the chemical during pregnancy. For this reason the Working Group will base its calculations on a 60-kg female applicator of child-bearing age.

A. Agricultural Exposure (Including Home and Garden)

The following inorganic arsenical pesticides are registered with the Environmental Protection Agency: arsenic acid, ammonium arsenite, arsenic trioxide, arsenic pentoxide, calcium arsenate, copper acetoarsenite, lead arsenate, sodium arsenite, sodium arsenate, and sodium pyroarsenate. Each of these pesticides, with the exception of sodium pyroarsenate, ammonium arsenite, and arsenic pentoxide, have agricultural or home uses. The Working Group will evaluate the oral, dermal, and inhalation exposure to those arsenical pesticides registered for agricultural or home use. Sodium pyroarsenate, ammonium arsenite, and arsenic pentoxide are used in the preservation of wood and will be discussed in subsequent portions of this report.

Because of the lack of data concerning exposure, the Working Group will make the following assumptions:

1. For analysis of oral exposure, the Working Group assumes that arsenic residues will be present at currently authorized tolerance levels. The Working Group realizes that residues found in or on raw agricultural commodities are typically lower than tolerance levels; however, because residues could lawfully be present at tolerance levels it is prudent to assume tolerance levels for regulatory pruposes. The arsenic contribution of each food will be calculated based on the average daily intake of the commodity as reported by Lehman (1962). Iwataki and Horiuchi (1959) sampled feces, urine, and blood of a normal (Japanese) population for arsenic. More than half of the arsenic detected (form not indicated) was found in the blood and urine. It is assumed, therefore, that 75% of all arsenic ingested will be absorbed;

2. For analysis of dermal exposure, it is assumed that the applicator will be contaminated with up to one pint of liquid (diluted for application per label instructions) and up to 10 grams of dust (in the case of dust formulations). It is further assumed that 10% of all arsenic in contact with the skin will be absorbed. Oehme (1972) states that inorganic arsenic is absorbed significantly through the intact skin; and

3. For analysis of inhalation exposure, it is assumed the applicator's breathing rate is 1.8 m^3/hr (active rate) and that all material inhaled will be absorbed. The Working Group also assumes that the applicator would spray for approximately seven hours per day.

(1) Sodium Arsenite

The Working Group has selected a product for analysis which contains 42.5% sodium arsenite as formulated (equivalent to 1.05 kg arsenic/gal). When diluted according to label directions, the solution contains 3.28 grams of arsenic per pint.

(a) Oral Exposure

In order to calculate the theoretical quantity of arsenic in the average diet, the Working Group will use the following formula, A x B x C x D / E in which:

A = the theoretical average daily intake of sodium arsenite in mg/kg, expressed as As_2O_3;

B = 1.5 kg, the average daily food intake (Lehman 1962);

C = 0.76, a correction factor for conversion from milligrams of the arsenic compound (As_2O_3) to total arsenic (the molecular weight of arsenic divided by the molecular weight of the compound);

D = 0.75% absorption factor; and

E = 60 kg. (Exposure is normally expressed in terms of milligrams of chemical per kilogram of body weight. Because teratogenic effects are of concern with inorganic arsenic all calculations of exposure will be based on exposure to a 60-kg woman.)

Therefore, for oral exposure to sodium arsenite (see Table 9), A x B x C x D / E = 0.051 mg/kg X 1.5 kg X 0.76 X 0.75 / 60 kg = 0.0007 mg/kg arsenic.

Table 9. Arsenic in Daily Diet Resulting From the Use of Sodium Arsenite

Food Item	Food Factor (percent of total diet)	Tolerance (mg/kg) [40 CFR 180.335]	Contribution to daily intake (mg/kg[a])
Beef[b]	4.60	0.7	0.0322
Horse[b]	data not available	0.7	—
Edible Offals[c]	0.69	2.7	0.01863
Grapes	0.32	0.05	0.00016
Total	5.61		0.05099 mg/kg

[a] Expressed as As_2O_3.
[b] Meat, fat, and meat by-products.
[c] Liver and kidney.

(b) Dermal Exposure

Assuming a one-pint exposure during mixing, handling, and application, an applicator would receive 3.28 grams X 0.1 (absorption) = 0.328 gm, or 328 mg; 328 mg / 60 kg = 5.47 mg arsenic/kg of body weight from dermal exposure to sodium arsenite.

(c) Inhalation Exposure

Using an estimate of 100 ug/m^3 [based on the concentration of arsenic in sodium arsenite and on extrapolation of data from Pinto et al. (1976)] for the concentration of metallic arsenic and the assumptions stated above, the inhalation exposure for a 7-hour day would be approximately 100 ug/m^3 X 1.8 m^3/hr X 7 hrs = 1,260 ug or 1.260 mg arsenic; 1.260 mg / 60 kg = 0.021 mg arsenic/kg of body weight from inhalation exposure to sodium arsenite.

Total theoretical exposure from sodium arsenite equals:

0.0007 mg/kg (through food)
5.47 mg/kg (due to dermal exposure)
0.021 mg/kg (due to inhalation exposure)
5.5 mg/kg

(2) Arsenic Acid

The Working Group has selected a representative arsenic acid product for analysis which contains 17.5% arsenic acid as formulated (equivalent to 1.5 pounds arsenic per gal). When diluted according to label directions, the solution contains 1.625 grams of arsenic per pint.

Table 10. Arsenic in Daily Diet Resulting From the Use of Arsenic Acid

Food Item	Food Factor (percent of total diet)	Tolerance (mg/kg) [40 CFR 180.180]	Contribution to daily intake (mg/kg[a])
cottonseed	0.5[b]	4	0.0316
Total	0.5		0.0316 mg/kg

[a] Expressed As_2O_3.

[b] Cottonseed is used in edible oils, margarine, etc. This food factor is an estimate and is not found in Lehman (1962).

(a) Oral Exposure

The theoretical quantity of arsenic in the daily diet due to arsenic acid (see Table 10) equals A x B x C x D / E (see oral exposure analysis for sodium arsenite), or 0.0316 mg/kg X 1.5 kg X 0.76 X 0.75 / 60 kg = 0.0005 mg/kg arsenic.

(b) Dermal Exposure

Assuming a one-pint exposure, an applicator would receive 1.625 grams x 0.1 (absorption) = 0.1625 gm, or 162.5 mg; 162.5 mg / 60 kg = 2.7 mg arsenic/kg of body weight from dermal exposure to arsenic acid.

(c) Inhalation Exposure

Using the estimate of 100 ug/m^3 [based on extrapolation of data from Pinto et al. (1976)] for the concentration of arsenic and the assumptions stated above, the inhalation exposure for a 7-hour day would be 100 ug/m^3 X 1.8 m^3/hr X 7 hr = 1260 ug, or 1.260 mg arsenic; 1.260 mg / 60 kg = 0.021 mg/kg arsenic from inhalation exposure to arsenic acid.

Total theoretical exposure from arsenic acid equals:

0.0005 mg/kg (through food)
2.7 mg/kg (dermal exposure)
0.021 mg/kg (inhalation exposure)
2.72 mg/kg

In addition to the exposure situations discussed above, the Working Group is also interested in arsenic exposure resulting from ginning of cotton treated with arsenic acid (as a desiccant). As a representative exposure situation, the Working Group will assess exposure to individuals living or working close to a cotton gin processing cotton treated with arsenic acid. Suta (1978) provided data showing the estimated arsenic in air concentrations at various distances from cotton gins. Arsenic concentrations were estimated to range from 0.003 ug/m^3 to 29 ug/m^3 for various cotton gins at various distances. Assuming all arsenic in air to be respirable and the concentration to be 29 ug/m^3, inhalation exposure for a 60-kg woman would be: 1.0 m^3/hr (breathing rate of a resting person) X 29 ug/m^3 (concentration of arsenic in air) / 60 kg = 0.48 ug/kg per hour. Assuming exposure to continue 24 hours per day, exposure would be 11.60 ug/kg, or 0.0116 mg/kg per day. These exposure estimates are for individuals living near cotton gins. Exposure to workers inside the gin would be significantly higher.

(3) Sodium Arsenate

(a) Oral Exposure

Although sodium arsenate has established tolerance levels for use on grapes, no sodium arsenate products are registered for such use; therefore, arsenic residues will not be present due to the use of sodium arsenate.

(b) Dermal Exposure

The Working Group has selected a representative sodium arsenate product containing 3% sodium arsenate as formulated (1.3% as arsenic) which is used in combination with sugar as an ant bait. Dermal exposure to the ant bait would generally be low; however, the directions call for saturating cotton with the 1.3% arsenic solution. In this case, the applicator could reasonably be expected to contact the wet cotton and be dermally exposed to as much as 30 gm (2 tablespoons) of solution. By calculation this would be 30 gm X 0.013 (% arsenic) = 0.39 gm, or 390 mg of arsenic metal. If 10% is absorbed by a 60-kg woman then the theoretical dermal dose would be: 390 mg X 0.10 = 39 mg; 39 mg / 60 kg = 0.65 mg/kg arsenic from dermal exposure to sodium arsenate.

(c) Inhalation Exposure

Since the product discussed above is used as a very dilute liquid, not a spray, inhalation exposure to sodium arsenate would not be significant.

Total theoretical exposure to sodium arsenate, therefore, would be 0.65 mg/kg (resulting from dermal exposure).

(4) Copper Acetoarsenite

The Working Group has selected a representative copper acetoarsenite (paris green) product which is used as a mosquito larvicide and contains 3.56% arsenic as the metal. The product is ready to use and does not require dilution. If applied aerially, minimal exposure to the applicator is expected. If applied by hand duster, dermal and inhalation exposure may result.

(a) Oral Exposure

Copper acetoarsenite has no registered food uses.

(b) Dermal Exposure

Wolfe et al. (1967) investigated dermal and inhalation exposure resulting from the use of insecticide dusts. Applicators using a power duster to apply 4% malathion dust to beans were exposed to 23 mg/hr dermally and 0.73 mg/hr by inhalation. Assuming the conditions and the equipment were similar, exposure from the use of copper acetoarsenite dust (containing 3.56% arsenic as the metal) can be calculated by incorporating a factor to correct for the difference between the concentration of pesticide in Wolfe's study (4%) and the arsenic concentration in copper acetoarsenite:

$$\text{Correction Factor } \frac{3.56\% \text{ (concentration of arsenic)}}{4\% \text{ (concentration of malathion)}} = 0.89.$$

Therefore, dermal exposure would be equal to:

23 mg/hr x 0.89 (correction factor) x 7-hours (length of work day) x 0.1 (absorption) / 60 kg = 0.24 mg/kg.

(c) Inhalation Exposure

Using Wolfe's information as discussed above, the inhalation exposure for a 7-hour work day is estimated to be:

0.73 mg/hr x 0.89 (correction factor) x 7 hours / 60 kg = 0.08 mg/kg.

Total theoretical exposure for copper acetoarsenite equals:

0.24 mg/kg (due to dermal exposure)
0.08 mg/kg (due to inhalation exposure)
0.32 mg/kg

(5) Calcium Arsenate

For the dermal and inhalation exposure analyses, the Working Group has selected a dust representative product containing 5% calcium arsenate (equivalent to 22.73 gm calcium arsenate per pound).

(a) Oral Exposure

Table 11. Arsenic in Daily Diet Resulting From the Use of Calcium Arsenate

Food Item	Food Factor (percent of total diet)	Tolerance (mg/kg) [40 CFR 180.192]	Contribution to daily intake (mg/kg[a])
Asparagus	0.23	3.5	0.0081
Beans	1.24	3.5	0.0434
Berries[b]	0.06	3.5	0.0021
Blackberries[c]	0.03	3.5	0.0011
Broccoli	0.19	3.5	0.0067
Brussels Sprouts	0.16	3.5	0.0056
Cabbage[d]	0.49	3.5	0.0172
Carrots	0.55	3.5	0.0193
Cauliflower	0.43	3.5	0.0151
Celery	0.76	3.5	0.0256
Corn	1.19	3.5	0.0417
Cucumbers	0.73	3.5	0.0256
Egg plant	0.32	3.5	0.0112
Kale[a]	0.14	3.5	0.0049
Melons	1.98	3.5	0.0693
Peppers	0.25	3.5	0.0088
Raspberries[c]	0.04	3.5	0.0014
Rutabagas	data not available		
Spinach	0.29	3.5	0.0102
Squash[f]	0.19	3.5	0.0067
Tomatoes	3.34	3.5	0.1169
Turnips	data not available		
Total	12.16		0.4409

[a] Expressed as As_2O_3.

[b] Includes blueberries, boysenberries, and huckleberries.

[c] Includes dewberries, loganberries, and youngberries.

[d] Includes kohlrabi.

[e] Includes pumpkins.

The theoretical quantity of arsenic in the daily diet (see Table 11) due to calcium arsenate equals A X B X C X D / E (see the oral exposure analysis for sodium arsenite) = 0.4409 mg/kg X 1.5 kg X 0.76 X 0.75 / 60 kg = 0.006 mg/kg.

(b) Dermal Exposure

Using Wolfe's observations as discussed in Section III. (4)(C) (Copper Acetoarsenite), dermal exposure would be equal to 23 mg/hr X 1.2 (correction factor for calcium arsenate) x 0.1 (absorption) X 7 hours X 0.38 (percentage of arsenic in calcium arsenate) / 60 kg = 0.12 mg/kg.

(c) Inhalation Exposure

Using Wolfe's information concerning inhalation, exposure would equal 0.73 mg/hr X 1.2 (correction factor) X 7 hours X 0.38 (percent arsenic) / 60 = 0.04 mg/kg.

Total theoretical exposure from calcium arsenate equals:

0.006 mg/kg (through food)
0.12 mg/kg (through dermal exposure)
0.04 mg/kg (due to inhalation exposure)
0.17 mg/kg

(6) Arsenic Trioxide: Oral, Dermal, and Inhalation Exposure

The Working Group has selected a representative arsenic trioxide product which contains 1.5% As_2O_3 and is used for control of mice, ants, and roaches. This bait is used full strength for rodents and diluted with meal for insects. The actual metallic arsenic concentration is 1.136%.

Due to the nature of the product, it is doubtful that oral or inhalation exposure would be significant. Carelessness and ordinary transfer problems could result in a dermal exposure of 2 tablespoons of solution on the hands. Two tablespoons contains approximately 30 gm of formulated product. Dermal exposure would then equal: 30 gms X 0.10 (10% absorption) X 0.0136 (% arsenic) = 0.0408 gm, or 40.8 mg arsenic; 40.8 mg / 60 kg = 0.68 mg/kg arsenic from dermal exposure to arsenic trioxide.

(7) Lead Arsenate

The Working Group has selected a representative lead arsenate product which contains 80% lead arsenate as formulated (equivalent to 0.03 pounds of lead arsenate/gallon) and when diluted according to label directions will contain 0.375 grams arsenic per pint.

Table 12. Arsenic in Daily Diet Resulting From the Use of Lead Arsenate

Food Item	Food Factor (percent of total diet)	Tolerance (mg/kg) [40 CFR 180.194]	Contribution to daily intake (mg/kg[a])
Apples	1.81	7[b]	0.1267
Apricots	0.12	7	0.0084
Asparagus	0.23	7	0.0161
Avocados	0.03	7	0.0021
Berries[c]	0.06	7	0.0042
Blackberries[d]	0.03	7	0.0021
Celery	0.76	7	0.0532
Cherries	0.17	7	0.0119
Cranberries	0.10	7	0.007
Currants[e]	0.12	7	0.0084
Eggplant	0.32	7	0.0224
Grapes	0.32	7	0.0224
Mangoes	data not available		
Nectarines	0.06	7	0.0042
Peaches	1.03	7	0.0721
Pears	0.32	7	0.0224
Peppers	0.25	7	0.0175
Plums (fresh)	0.23	7	0.0161
Quinces	data not available		
Raspberries[d]	0.04	7	0.0028
Strawberries	0.19	7	0.0133
Tomatoes	3.34	7	0.2338
Citrus Fruits	4.00	7	0.04
total	13.53	1[f]	0.7071

[a] Expressed as combined lead.

[b] Equivalent to 3.5 ppm As_2O_3.

[c] Includes huckleberries, boysenberries, and blueberries.

[d] Includes dewberries, loganberries, and youngberries.

[e] Includes gooseberries.

[f] Equivalent to 0.5 ppm As_2O_3.

(a) Oral Exposure

The theoretical quantity of arsenic in the daily diet due to lead arsenate (see Table 12) equals A X B X C X D / E (see oral exposure analysis for sodium arsenite) = 0.354 mg/kg (equivalent to 0.707 combined lead) X 1.5 kg X 0.76 X 0.75 / 60 = 0.005 mg/kg arsenic.

(b) Dermal Exposure

Assuming a one-pint exposure, an applicator would receive 0.375 gm X 0.1 (10% absorption) = 0.0375 gm, or 37.5 mg; 37.5 mg / 60 kg = 0.63 mg/kg arsenic from dermal exposure to lead arsenate.

(c) Inhalation Exposure

Using the estimate of 100 ug/m^3 [based on extrapolation of data from Pinto et al. (1976)] for the concentration of arsenic, and the assumptions stated above, the inhalation exposure could be 100 ug/m^3 X 1.8 m^3/hr X 7 hr = 1,260 ug, or 1.260 mg arsenic; 1.260 mg / 60 kg = 0.021 mg/kg arsenic from inhalation exposure to lead arsenate.

Total theoretical exposure from lead arsenate equals:

0.006 mg/kg (through food)
0.63 mg/kg (dermal exposure)
0.021 mg/kg (inhalation exposure)
0.66 mg/kg

B. Exposure From Treatment of Wood With Arsenical Wood Preservatives and Subsequent Use of Such Products

Arsenical salts are used to protect a variety of wood products against various pests. Arsenic treated wood is used in the construction of homes, in utility poles, fence posts, marine piers, pilings, etc. The majority of wood is treated in closed cylinders under pressure, although there are instances where the preservatives are painted on wood or wood is soaked in solutions containing arsenic.

There are three basic arsenical wood preservatives of commercial importance. These are Chromated Copper Arsenate (CCA), Ammonical Copper Arsenate (ACA), and Fluor Chrome Arsenate Phenol (FCAP). These three wood preservatives are various mixtures made, in part, from either ammonium arsenite, arsenic trioxide (both trivalent arsenicals), arsenic acid, arsenic pentoxide, sodium arsenate, or sodium pyroarsenate (all pentavalent arsenicals). During the formulation process all trivalent arsenic is oxidized to pentavalent arsenic (AWPI 1977).

In the past, arsenical wood preservatives have been referred to under many different names. The various names and relationships of chemical constituants are cross-referenced in Table 13. The percentages listed indicate the relative proportion of active ingredients in the formulated products. The percentages listed are on the oxide (solids) basis. Table 14 lists typical arsenical formulations available.

Table 13.[a]

CHROMATED COPPER ARSENATE (CCA, Cr-Cu-As, CKA)

Type	Chromium as CrO_3	Copper as CuO	Arsenic as As_2O_3	Common Name
A	65.5%	18.1%	16.4%	CCA-A CCA-Type I Ascu Greensalt-K Erdalith
B	35.3%	19.6%	45.1%	CCB-B CCA-Type II Boliden Salt K-33 Lahontuho K-33
C	47.5%	18.5%	34.0%	CCA-C Tenalith C Celcure AP Chrom- Ar-Cu Tancas C Wolman CCA K-33-C

AMMONICAL COPPER ARSENATE (ACA, Chemonite)

Copper as CuO	Arsenic as As_2O_3	Ammonia NH_3	Common Name
49.8%	50.2%	weight of NH_3 1.5-2.0 times weight of CuO	CCA Chemonite

FLUOR CHROME ARSENATE PHENOL

Fluoride as F	Chromium as CrO_3	Arsenic As_2O_3	Dinitrophenol of Sodium Pentachlorophenate	Common Name
22%	37%	25%	16%	FCAP Tanalith U CFA Osmosalts

[a] AWPI (1977)

Table 14. Representative Formulations of Pesticide Products Used in the Pressure Treatment of Wood

CCA-Type A		CCA-Type B	
Potassium Dichromate	53%	Arsenic Pentoxide*	34%
Copper Sulfate	32%	Copper Oxide	14.5%
Arsenic Pentoxide*	10%	Chromic Acid	25.6%
Inerts	5%	Inerts	25%
*(Arsenic as the metal	5.64%)	*(Arsenic as the metal	22.17%)

CCA-Type C	
Arsenic Pentoxide*	26.9%
Sodium Dichromate	42.6%
Copper Sulfate	25.5%
Inert	5.9%

*(Arsenic as the metal 14.09%)

Ammonical Copper Arsenate (ACA)+	
Arsenic Trioxide*	37%
Copper Metallic	36%

*(Arsenic as the metal 28.12%)

+This is not sold as a formulated product. These chemicals are used to produce an intermediate which is diluted on site to prepare the dilute treating solution. There are no formulated products for ACA preservatives intended for industrial use.

Fluor Chrome Arsenate Phenol	
Sodium Chromate	34.2%
Sodium Floride	27.5%
Disodium Arsenate*	23.8%
Sodium Pentachlorophenate	7.8%
Sodium Salts of other chlorophenol & related compounds	1.7%
Inert	5.0%

*(Arsenic as the metal 9.59%)

The following is an example of activities associated with industrial wood treatment situations although individual treatment facilities may vary their procedure. In the industrial situation arsenical formulations (concentrates) are delivered as dusts, liquid concentrates, or pastes. The concentrates are dumped or otherwise metered and mixed with water to form dilute treating solutions of 0.75 to 6.0%, depending on the intended end-use of the treated wood.

Lumber to be treated is stickered (stacked so as to provide spaces for fluid circulation) onto a tram either by machine or hand. The loaded tram is moved (e.g., by rail) into the treatment cylinder. The cylinder door is closed and air in the cylinder evacuated. The cylinder is then filled with treating solution from storage tanks. Pressure is applied to achieve maximum impregnation, a process which may require up to eight hours. The cylinder is emptied by air pressure upon completion of the treatment cycle.

Following removal of the treating solution, the cylinder door is unbolted and pulled open manually. The charged lumber is pulled from the cylinder on its tram to a concrete pad where drippings are collected for reuse. The treated product is removed from the tram by forklift truck for air drying in the yard or kiln. The treated lumber is unstickered by laborers who also stamp on the trademark and stack the lumber for shipment.

Exposure from treatment of wood or its subsequent use can be divided as follows: large scale industrial situations; intermittent application to wood during on-site construction;

exposure from handling, sawing, fabrication, etc., of treated wood products; and exposure to individuals living or working in dwellings containing arsenic-treated wood.

(1) Large Scale Industrial Situations

The regulation of industrial situations to insure worker safety is normally the responsibility of the Occupational Safety and Health Administration. However, Section 4(b)(1) of the Occupational Safety and Health Act (29 U.S.C. S653(b) (1)) provides that "[n]othing in this Act shall apply to working conditions of employees with respect to which other Federal Agencies...exercise statutory authority to prescribe or embrace standards or restrictions affecting occupational safety or health." Since the industrial treatment of wood with arsenic preservatives involves the application of a pesticide, EPA has assumed regulatory responsibility under FIFRA. EPA regulation of arsenic in this use pattern has the effect of pre-empting OSHA. Exposure to inorganic arsenic in the industrial setting could arise through the inhalation and/or dermal routes.

(a) Inhalation Exposure

Several studies have been conducted to determine the amount of arsenic in air in or around treatment plants during the treatment and handling of treated wood (Table 15). Most of this data was presented by Dr. Robert Arsenault during OSHA public hearings in April 1975 on the proposed exposure standard for inorganic arsenic. Dr. Arsenault noted that "a large amount of the data was obtained during damp winter conditions so that the numbers (concentration of arsenic in air) shown are conservative estimates. In dry summer weather, the airborne arsenic from handling lumber, such as in air seasoning yards and during unstickering, would be much higher" (Arsenault 1975).

Table 15. Arsenic in Air During Treatment and Handling of Wood[a/]

Chemical	Activity	Arsenic Concentration in Air (mg/m^3)	Comment
ACA	changing retort charge	0.012	
ACA	boring of treated wood to assay for arsenic	0.001	
ACA	mixing treatment charges, moving barrels containing arsenic to door of mixer, dump chemical, scrape chute	0.020 0.025	light rain
ACA	hand stickering of treated wood	0.006 0.004 0.004	light rain
ACA	loading treated poles on flat car	0	
ACA	wiring and strapping treated lumber on flat car	0.007 0.002	
ACA	loading and stickering of treated poles in kiln driers	0 0.002	light rain
ACA	machine stickering of treated plywood	0.003 0.0034 0.002	
ACA	hand unstickering of treated lumber	0.020 0.007 0.055	
ACA	unloading of kiln drier; moving material from kiln to shed	0.001 0.005 0.007	
ACA	five feet down wind from stack of air drying poles	0.002 0.003 0.004	
CCA	exhaust of drying kiln fully charged with treated lumber	0.0042	sample was taken at the exhaust of kiln by inserting probe directly into the gas stream as it was exhausted

a/ Data from Arsenault (1975).

Table 15 (continued)

Chemical	Activity	Arsenic Concentration in Air (mg/m^3)	Comment
CCA	surface area of a bundle of treated lumber just out of the retort	0.0014	
CCA	treating wood	0.008	
CCA	stacking dry treated lumber	0.002	
CCA-B	treated lumber stored outside	0.001	
CCA-B	mixing/treating area	0.001	no mixing underway no forced ventilation
CCA-B	changing the charge of treatment tank	0.03	
CCA-C	mixing preservative	0.05	concentrate mixed in open tanks
CCA-C	in lumber yard of treatment plant	0.01	
CCA-C	stacking dry treated plywood	0.01	
CCA-C	stacking dry treated plywood	0.22	
CCA-C	handling treated lumber in lumber yard	0.0018	
CCA-C	stickering and unstickering of treated wood	0.007	
CCA-C	locomotive operator and helper moving treated wood from treatment site site	0.0001	
CCA-C	taking test sample (boring) of treated wood at treatment site	0.0001	

Table 15 (continued)

Chemical	Activity	Arsenic Concentration in Air (mg/m^3)	Comment
CCA-C	treater loading wood	0.0001	
CCA-C	mixing preservative from dry powder concentrate	0.77 (8 hour TWA for 2 mixes 0.016)	one or two mixes/ day; each mix takes 8.8 to 9 min, operator handles dry wood the remainder of the day, opera- used respirator, gloves, and apron

The highest arsenic-in-air values (0.77 mg/m^3) were detected when workers mixed preservatives from dry preservative concentrates. This activity, however, does not continue for extended periods of time. As noted by the author, one or two mixes are prepared each working day with each mixing operation lasting 8.8 to 9.0 minutes. The 8-hour time-weighted average (TWA) for this activity would be approximately 0.016 mg/m^3.

The next highest arsenic-in-air value (0.22 mg/m^3) was detected when workers stacked dry, treated plywood. In order to calculate the theoretical inhalation exposure resulting from this activity, the Working Group assumes that the workers' breathing rate is 1.8 m^3/hr; that all inhaled arsenic will be respirable; that all arsenic reaching the lung will be absorbed; and that the worker will spend the entire working day (8 hours) in the contaminated areas.

Therefore, 0.22 mg/m^3 X 1.8 m^3/hr (breathing rate) = 0.396 mg arsenic/hr; 0.396 mg/hr X 8 hours per day = 3.168 mg arsenic inhaled per day. If we assume the worker to be a 60-kg woman, then exposure would be 3.168 mg / 60 kg = 0.05 mg/kg per day.

The Pacific Biomedical Research Center, University of Hawaii (PBRC Undated), conducted urine analysis studies of workers involved in the industrial application of arsenical (CCA) preservatives. The purpose of the study was to estimate arsenic exposure by monitoring arsenic concentration in urine. The study population was divided into two groups "reference" and "exposed." The reference group corresponded to workers employed in the wood treating industry whose contact with CCA preservatives was "incidental or ambiguous such as clerks, salesman, chemists, plant superintendents, etc." The author concluded there was not a significant difference in residue levels between the "exposed" and "reference" groups. The author did not, however, compare the arsenic concentration of the "reference" group to that of the local population not associated with the preservative (Letter 1978). Mean arsenic values of individuals in the study were as follows: "Exposed" (42 individuals), 0.074 ppm; "Reference" (12 individuals), 0.070 ppm.

The author indicated there may have been an incidental exposure to arsenic by the "reference group." The author also indicated that the plant was almost entirely in the open (Letter 1978).

(b) Dermal Exposure

Little data is available with which to assess potential dermal exposure to arsenic in the industrial situation. If we assume, however, that the actual treatment of wood occurs in closed cylinders under pressure and that there is no exposure to the worker during treatment, then dermal exposure will be limited either to handling preservative concentrates and dilute treating solutions, or to handling wet treated wood after treatment. The following analysis assesses the potential dermal exposure resulting from the use of dust and liquid concentrate formulations.

(i) Handling Preservative Concentrates and Dilute Treating Solutions

a. Dust Formulations

Fluor Chrome Arsenate Phenol (FCAP) preservative formulations are shipped as dusts. The Working Group assumes that workers involved in dumping dust concentrates to prepare dilute treating solutions will each be contaminated with up to 10 grams of dust concentrate. Representative FCAP formulations contain 9.59% arsenic as the metal. The

Working Group assumes that 10% of all dust coming in contact with the worker will be absorbed. Therefore, 10 gm (exposure) X 0.0959 (% concentration of arsenic as metallic) = 0.959 gm, or 959 mg; 959 mg X 0.1 (% absorbed) = 95.9 mg. If we assume the worker to be a 60-kg woman, exposure would be 95.9 mg / 60 kg = 1.6 mg/kg arsenic exposure to FCAP concentrate wood preservatives.

b. Liquid Formulations

CCA preservatives are often shipped as liquid concentrates. The Working Group assumes workers involved in preparing dilute CCA solutions could be contaminated with up to 20 ml of liquid concentrate (enough to wet both hands). Representative CCA formulations contain 27.17% arsenic as metallic. The Working Group assumes 10% of all arsenic coming in contact with the worker will be absorbed. Therefore, 20 ml (20 gms) X 0.27 (% arsenic as metallic) = 5.4 gm arsenic reaching the body; 5.4 X 0.1 (% absorption) = 0.54 gm, or 540 mg. If we assume the worker to be a 60-kg woman, exposure would be 540 mg / 60 kg = 9.0 mg/kg arsenic resulting from exposure to CCA concentrate wood preservatives.

Klemmer et al. (1975) studied the amount of arsenic in house dust of persons employed in the wood preserving industry and persons living in homes containing arsenic treated wood. One member of the study group was actually involved with handling CCA formulated products (Memo 1978b). This home did not contain treated wood and yet contained 1,080 ppm arsenic in house dust, while homes whose residents did not work with arsenic and did not contain treated wood showed levels of 1.1 to 9.1 ppm arsenic in dust. The Working Group assumes the 1,080 ppm arsenic in dust resulted from occupational exposure to CCA wood preservatives and documents the significant nature of worker exposure to arsenic resulting from industrial use of arsenical wood preservatives.

(ii) Handling Wet Treated Wood After Treatment

The Working Group assumes workers in plants using arsenic in the treatment of wood will handle wet, treated wood without gloves or specialized clothing (Memo 1978b) and that the concentration of arsenic on the surface of the wood will be that of the treating solution. If gloves are worn, however, it is assumed these gloves would be made of cloth, would become saturated with treating solution, and would provide no protection against dermal exposure. Treating solutions vary from 0.75 to 6% active ingredient depending on the intended end use of the treated wood (AWPI 1977). Table 14 lists representative preservative formulations. Assuming that the treating solution used will contain 6% active ingredient, the amount of arsenic as metallic in representative dilute treating solutions will be 1.33% for CCA, 1.69% for ACA, and 0.57% for FCAP.

Assuming that the treated wood removed from the treatment cylinders will be dripping wet, that the worker will be contaminated with up to 20 ml (enough to wet both hands) of dilute treating solution, and that 10% of this arsenic-contaminated solution will be absorbed, and using the figure of 1.69% metallic arsenic in dilute Ammonical Copper Arsenate preservatives as an example, the dermal exposure resulting from handling wet treated wood will be as follows: 20 ml (20 gm) X 0.017 (% arsenic as metallic) = 0.34 gm, or 340 mg arsenic reaching the body; 340 mg X 0.1 (% absorption) = 34 mg. If we assume the worker to be a 60-kg woman, the dermal exposure will be 33.8 mg / 60 kg = 0.57 mg/kg resulting from exposure to wet treated wood.

(2) Intermittent Application to Wood During On-Site Construction

Two wood preservative products (containing 7.7% ammonium arsenite, equivalent to 3.26% arsenic) are available for use during the construction of structures built with pressure-treated wood. The products are intended for use on freshly cut ends of previously treated lumber. The directions instruct the applicator (i.e., carpenter) to apply several coats of preservative with a brush or rag mop and to wash off the solution to avoid staining the hands. Because these products are applied as a viscous liquid, and not as a spray, inhalation exposure to ammonium arsenite would be minimal.

Assuming 20 ml (enough to wet both hands) of solution will reach the skin and or clothing and that 10% will be absorbed before the skin is washed, the applicator could receive 20 ml (20 gm) X 0.033 (% concentration of arsenic) X 0.1 (% absorption) = 0.066 gm, or 66 mg arsenic.

Assuming the applicator to be a 60-kg woman, the applicator would receive 66 mg / 60 kg = 1.1 mg/kg arsenic from dermal exposure to ammonium arsenite.

(3) Exposure from Handling, Sawing, Fabrication, etc., of Treated Wood Proudcts

Exposure to inorganic arsenic under these conditons would arise through the inhalation and/or dermal routes.

(a) Inhalation Exposure

Several studies have been conducted to determine the amount of arsenic in air during cutting and building operations involving treated wood. Table 16 indicates the results from these studies.

The highest value recorded was 0.7 mg/m^3 during the cutting of ACA-treated plywood using a router. The author commented that these results were obtained after only 5 minutes of cutting. In order to conduct this analysis the following assumptions are made:

1. The worker will be involved in sawing related activities for 8 hours a day;
2. The air will not become saturated with arsenic particles in only 5 minutes. The arsenic in air level will be at least double the five minute value, or 1.4 mg/m^3, if this activity continued throughout the working day;
3. The workers breathing rate will be 1.8 m^3/hr;
4. 25% of the arsenic containing dust will be respirable;
5. All arsenic reaching the lung will be absorbed;
6. All of the non-respirable arsenic (not absorbed through lung tissue but present in respiratory system) containing dust will enter the gastro-intestinal tract;
7. Of the 75% non-respirable dust, 75% will be absorbed through the GI tract; and
8. The worker will spend the entire working day in the contaminated area.

Table 16. Arsenic Concentrations in Air During Cutting and Building Operatio

Chemical	Activity	Arsenic Concentration in Air mg/m^3)	Comments
ACA	sawing treated wood indoors (10" table saw)	0.24 0.048 0.042 0.062	results obtained during the rainy season and would be much higher in drier months
ACA	shaving the ends of treated poles	0.019 0.123 0.249	
ACA	cutting treated plywood with a router, plywood treated with 0.6 pcf	0.07-0.70	after cutting 5 min
ACA	cutting plywood with skill saw, plywood treated with 0.6 pcf	0.36	after cutting through feet of board (author notes the respirable fraction was 5.3%, or 0.019 mg/M^3)
ACA	handling and hammering treated wood	0.01-0.033 (TWA) 0.01-0.024)	author notes that these values include some cutting opperations
CCA-B	sawing treated studs	0.038	no forced ventilation in building
CCA-B	Construction of foundation panels using treated wood (assembly area)	0.012	no forced ventilation in building
CCA-B	during assembly of treated wood foundations	0.012	no forced ventilation in building
CCA-C	cutting plywood containing 0.6 pcf using a 6" fine-toothed plywood finish blade	0.071 0.097 0.015	this blade produces less dust per cut than a general purpose blade; data collected indoors, no external ventilation

a/ Data from Arsenault (1975).

Therefore 1.4 mg/m^3 X 1.8 m^3/hr (breathing rate) = 2.52 mg/hr; 2.52 mg/hr X 8 hours/day = 20.16 mg/day; 20.16 mg X 0.25 (% respirable) = 5.04 mg reaching lungs; 20.16 mg X 0.75 (% non-respirable) = 15.12 mg/day to GI tract; 15.12 mg X 0.75 (75% GI absorption) = 11.34 mg absorbed through GI tract. Total theoretical arsenic exposure would be:

 5.04 (absorbed through lung)
11.34 (absorbed through GI tract)
16.38 mg/day total arsenic exposure per day.

If we assume the worker to be a 60-kg woman, exposure would be 16.38 mg / 60 kg = 0.27 mg/kg.

(b) Dermal Exposure

In order to determine the amount of arsenic which can enter the system, it is first necessary to determine how much arsenic is available on the surface of the treated wood. Several studies are available showing the amount of arsenic removed when dry, treated wood is wiped with a sponge, wet human hand, dry human hand, etc. Table 17 summarizes that data available on arsenic content of wood dust, splinters, etc. It is also desirable to determine the amount of arsenic which can be leached from wood when exposed to damp or flooded conditions. Table 18 summarizes the available data showing the amount of inorganic arsenic which can be leached from treated wood. If the treated wood, e.g. as used in houses, is subjected to water from rain, flooding, etc., this additional arsenic would then be available and of importance when considering dermal exposure.

A representative exposure situation would be that resulting from the construction of homes using arsenic-treated wood. A typical activity would be the carrying, positioning, and nailing of treated plywood in the construction of floors of domestic dwellings. For purposes of this analysis the following assumptions are made:

1. The worker will work with four by eight foot sheets (32 sq ft) of arsenic-treated plywood;
2. The treated wood will be positioned and nailed at the rate of 7 sheets per hour;
3. The worker will work with the treated wood for 8 hours per day;
4. The worker will come in contact with 15% of the surface of the wood; and
5. The worker's hands will become damp with perspiration and could remove up to 0.529 mg/ft^2 arsenic (Dreher 1974).

Therefore, the worker will handle 224 sq ft of wood per hour and 1,792 sq ft during the course of an 8-hour day. If the worker's skin comes in contact with 15% of the wood, then the worker would contact 15% X 1,792 sq ft, or 268.8 sq ft of arsenic-treated wood per day. As shown by Dreher (1974) [see Table 17], a damp human hand can remove up to 0.529 mg arsenic per square foot of wood. If the worker contacts 268.8 sq ft, a total of 142.2 mg arsenic will come in contact with the skin per day. If the worker is wearing short pants and kneels on the wood during construction exposure would be higher. Assuming 10% absorption, 14.22 mg of arsenic will enter the body. If we assume the worker to be a 60-kg woman, exposure would then be calculated as 14.22 mg / 60 kg = 0.24 mg/kg resulting from contact with arsenic-treated wood. Fahlstrom et al. (1967) studied the leaching rate of CCA-treated wood samples. The authors found that treated wood leached with distilled water liberated 10.5% of its arsenic in two days. It is possible that dermal exposure to treated wood as discussed above would be significantly higher if treated wood was subjected to rain prior to or during construction.

Table 17. Arsenic Content of Dust, Splinters, Deposites, etc., from the Surface of Plywood Pressure-treated with Chromated Copper Arsenate (CCA) Wood Preservatives

Dwelling or Sample Number	Procedure Used to Assay for Arsenic- or Description of Sample	Amount of Arsenic Removed	Comment	Reference
A[a]	Splinters	310 ppm >4,540 ppm 2,450 ppm	taken from treated wood in homes	NCMA (1976)
A	Wood Scraping	>190 ppm	"	"
A	Greenish salt-like Formation on Wood	3,050 ppm	"	"
B[a]	Splinter	>460 ppm >420 ppm >340 ppm >440 ppm	"	"
B	White Deposit	>460 ppm	"	"
B	Dust Around knot Hole	>210	"	"
1	Splinter	12,000 ppm	"	Sleater and Berger (1977)
2	Splinter	15,000 ppm	"	"
4	Splinter	10,000 ppm	"	"
7[a]	Splinter	10,000 ppm	"	"
8[a]	Splinter	10,000 ppm	"	"

[a] Homes A and 7 are the same; Homes B and 8 are the same.

> Exceeded the limit of detection.

Table 17 (Continued)

elling or mple Number	Procedure Used to Assay for Arsenic or Description of Sample	Amount of Arsenic Removed (mg/sq ft)	Comment	Reference
-	Wood wiped with dry tissue	0.078-0.22	Dry wood	Dreher (1974)
-	Wood wiped with damp sponge	0.109-0.53		"
-	"	0.236-0.252	Wood soaked in quiescent water for 24 hours, air dried and wiped	"
-	Dry wood wiped with a dry human hand	0.0075-0.252	Wood - 2 wks old	"
	"	0.005-0.0085	Wood - 2 yrs old	"
-	Dry wood wiped with a damp human hand	0.115-0.278	Wood - 2 wks old	"
-		0.255-0.529	Wood - 2 yrs old	"
-	Wood wiped with a dry human hand	0.0005-0.00095	Wood - 2 wks old Wood hosed down prior to wipe	"
-	"	0.005-0.015	Wood - 2 yrs old Wood hosed down prior to wipe	"

Table 17 (Continued)

Dwelling or Sample Number	Procedure Used to Assay for Arsenic or Description of Sample	Amount of Arsenic Removed (mg/sq ft)	Comment	Reference
-	Wood wiped with damp human hand	0.071-0.082	2-wk-old wood hosed down prior to wipe	Dreher (1974)
-		0.097-0.185	2-yr-old wood hosed down prior to wipe	"
7	Wood wiped with dry tissue	0.004	Taken from treated wood in home	Sleater & Berger (1977)
8	"	0.005	"	"
9	"	0.002	"	"
10	"	0.009	"	"
11	"	0.128	Taken from treated wood in home; whitish deposit where reinforcing rod meets wall	"

Table 18. The Amount of Arsenic Leached From Treated Wood

Type Preservative	Size of Wood Sample	Leaching Material	Duration of Test	Amount Leached	Comments	Reference
CCA (FDN)	3x5x5/8"	deionized water	1 day	5.3 ppm (0.12 mg/in)	0.6 pcf	Memo (1973)
			3 days	10 ppm (0.33 mg/in)		
			7 days	13.3 ppm (0.30 mg/in)		
			28 days	45.5 ppm (1.03 mg/in)		
CCA (LP22)	3x5x5/8"	deionized water	1 day	3.0 ppm (1.03 mg/in)	0.4 pcf	Memo (1973)
			3 days	6.6 ppm (0.15 mg/in)		
			7 days	9.66 ppm (0.22 mg/in)		
			28 days	23.3 ppm (0.53 mg/in)		
Control	3x5x5/8"	deionized water	1 day	0.016 ppm (0.0004 mg/in)	control	Memo (1973)
			28 days	0.023 (0.0005 mg/in)		
CCA	1.5x5x0.125"	distilled water	2 days	0.4%	1.37 pcf	Fahlstrom et al. (1967)
			14 days	0.5%		
			2 days	3.1 %	1.22 pcf	
			14 days	8.2%		

Table 18 (Continued)

Type Preservative	Size of Wood Sample	Leaching Material	Duration of Test	Amount Leached	Comments	Reference
CCA	1.5x5x0.125"	distilled water	2 days	10.5%	0.796 pcf	Fahlstrom et al. (1967)
			14 days	20.75%		
			2 days	19.65%	1.29 pcf	
			14 days	35.%		
FCAP	2x1x0.5"	distilled water	3/8 hr	0.8%	0.124 pcf	McCarthy and Wilson (1957)
			22 7/8 hr	4.5%		
			3.95 days	10.0%		
			127.94 days	35.4%		
ACA	2x1x0.5"	distilled water	3/8 hr	6.5%	0.555 pcf	McCarthy and Wilson (1957)
			22 7/8 hr	18.8%		
			3.95 days	29.3		
			127.94 days	55.2%		
CCA	2x1x0.5"	distilled water	3/8 hr	0.0%	0.124 pcf	McCarthy . . Wilson (1957)
			22 7/8 hr	0.1%		
			3.95 days	0.1%		
			127.94 days	2.8%		
CCA	60x75x100 cm	tap water	10 minutes scrubbed with brush - from round surface	0.07-0.39 mg/sq ft	0.94 pcf (approx)	Johanson and Dale (1973)
			10 minutes scrubbed with brush - from intact end area	1.15-2.44 mg/sq ft		

(4) Exposure to Individuals Living and/or Working in Dwellings Containing Arsenic-Treated Wood

Exposure to inorganic arsenic resulting from living or working in dwellings containing arsenic-treated wood occurs through the inhalation and dermal routes.

(a) Inhalation Exposure

Two studies [NCMA (1976) and Sleater and Berger (1977)] are available which discuss the amount of arsenic in air of dwellings containing arsenic-treated wood. Table 19 summarizes the results from these studies.

The NCMA (1976) study was conducted by an independent testing laboratory (Froehling & Robertson, Inc.) for the National Concrete Masonry Association. In this test the air of two homes was sampled using a high volume air sampler fitted with an 8 x 10 inch fiberglass filters. A volume of 4,860 cubic feet of air was passed through the filters at each location. The tests were conducted during normal living activities at each location. Residents were in and out, cleaning, cooking, etc. Chemical analysis of the samples was conducted using the silver diethyldithiocarbamate method.

The Sleater and Berger (1977) study was conducted by the National Bureau of Standards (NBS). In this study the air of eight homes were sampled for arsenic content. The samples were collected using high volume air samplers fitted with fiberglass or paper filters of approximately 0.3 micron porosity. Between 200 and 2,000 cubic meter of air per site was sampled depending upon accessibility. Chemical analysis of the samples was conducted using the silver diethyldithiocarbamate method.

Both homes monitored by Froehling & Robertson (NCMA 1976) were also monitored by NBS (Sleater and Berger 1977), with markedly different results. Froehling & Robertson (NCMA 1976) monitored the houses on May 27, 1976, and recorded arsenic in air values of 0.6 to 3.6 mg/m^3. NBS monitored the houses in mid-December and mid-March of 1976 and recorded arsenic in air values of 0.002 to 0.031 ug/m^3.

In its report NBS commented concerning the markedly varying results of the NBS versus Froehling & Robertson. Of the differences in findings the authors note, "The disparity between the arsenic in air levels reported [refering to the NBS figures] cannot be explained at this time. It is clear the NBS has not confirmed the findings reported by NCMA, but neither has NBS refuted these findings." The authors note that a thorough cleaning of the residence prior to their visit could explain the lower levels of arsenic found by NBS. The results in Table 19 represent data from only seven homes containing arsenic-treated wood. A survey of more treated homes could reveal much higher or lower levels of arsenic in air.

In order to calculate the theoretical arsenic exposure through inhalation, the following assumptions are made:

1. breathing rate to be 1.0 m^3/hr (resting mode) or 1.8 m^3/hr (active mode);

2. 100% of all arsenic in air will be respirable. A figure of 25% respirable was used when calculating inhalation exposure resulting from the cutting of arsenic-treated wood as discussed earlier. When cutting wood the fine particles of wood containing arsenic would become airborne but would probably not be completely respirable. In the case of a domestic dwelling, however, arsenic-containing dust would be of much smaller particle size and could therefore be respirable;

3. 100% of all respirable arsenic will be absorbed.

4. The resident of the dwelling will be present for 16-24 hours per day. It should be noted that, in the case of teratogenicity, the period of time during which the developing fetus is at risk may be

relatively short. Hood and Pike (1972), Hood et al. (1977; undated), etc., have demonstrated that arsenic exposure on one or two critical days of organogenesis will result in malformations. While it would be unreasonable to assume that a woman of child bearing age would remain in the arsenic treated home for 24 hours, day in and day out, it is not unreasonable to assume the woman to be present for any one continuous 24 hours period. If the developing fetus were to undergo a critical phase of organogenesis while the mother was present in a house containing arsenic-contaminated air it is not unreasonable to assume this exposure to continue for up to 24 hours.

Using the figure of 3.6 ug/m^3 (NCMA dwelling A) as a worst case situation and assuming the woman to be present in the house for 24 hours and that 16 of the 24 hours will be in the active mode (respiratory rate of 1.8 m^3/hr) and 8 hours in the resting mode (1.0 m^3/hr) exposure would be:

1.8 m^3/hr (active breathing rate) x 16 hours = 28.8, plus 1.0 m^3/hr (resting rate) x 8 hours = 36.8m^3/hr; 36.8 m^3/hr x 3.6 ug/m^3 (arsenic content in air) = 132.5 ug/24 hours or 0.132 mg/24 hours.

Assuming the resident to be a 60-kg woman, the resident would be exposed to 0.133 mg/60 kg = 0.002 mg/kg/day as a result of breathing arsenic-contaminated air.

Using the figure of 0.002 ug/m^3 (Sleater and Berger dwelling 8) as a best case situation and assuming the woman to be present in the house for 16 hours and that 8 hours of the 16 will be in the active mode (respiratory rate of 1.8 m^3/hr) and 8 hours in the resting mode (1.0 m^3/hr), exposure would be 7 x 10^{-7} mg/kg/day (trace).

Table 19. Arsenic in air of building constructed with wood pressure-treated with arsenical wood preservatives

Dwelling Number	Arsenic in Air (ug/m^3)	Comments	Reference
1	0.012	Treated wood exposed	Sleater and Berger (1977)
1	0.031	Treated wood covered	
2	0.016	Treated wood exposed	
2	--	Treated wood covered	
3	0.011-0.007	Masonry Constructed Foundation	
7	0.013	Treated Wood Exposed	
7	0.002	Treated Wood Covered	
8	0.019	Treated Wood Exposed	
8	0.002	Treated Wood Covered	
9	0.002	Treated Wood Exposed	
9	0.003	Treated Wood Covered	
10	0.005	Treated Wood Covered	
10	--	Treated Wood Covered	
11	0.003	Treated Wood Exposed	
11	0.003	Treated Wood Covered	
1-11	0.002	Average arsenic content of outside air	
A*	3.6	No Comment	NCMA (1976)
B*	0.6	No Comment	

a/ In some cases both NBS and NCMA examined the same dwellings; home A and 7 are the same dwelling, as are B and 8.

Table 20. Arsenic in dust of homes containing arsenic-treated wood

Dwelling Number	Arsenic Content of dust (ppm)	Comment	Reference
1	211	Exposed Plywood	Sleater and Berger (1977)
1	2	Covered Plywood	
3	28-27	Masonry Construction	
4	53	Covered Plywood	
6	1267	Exposed Plywood	
6	7	Covered Plywood	
7	123-354	Exposed Plywood	
8	61-69	Exposed Plywood	
9	138	Exposed Plywood	
0	18	Covered Plywood	
11	10	Exposed Plywood	
A	18 32 >440	No Comment	NCMA (1976)
B	>210 1640	No Comment	
-	11 21 13 17 23	From vacuum cleaner sweepings	Klemmer et al. (1975)

(b) Dermal Exposure

Dermal exposure could arise from direct contact with treated wood, or contact with arsenic-containing dust produced from or by treated wood.

(i) Direct Contact with Treated Wood

Tables 17 and 18 summarize relevant data concerning the amount of arsenic available in splinters, on the surface of treated wood, and the amount of arsenic which can be leached by water. The highest rates are listed in Table 21.

Table 21.

Source	Amount of arsenic	Comment	Reference
Greenish salt-like formation on wood	3,050 ppm	taken from treated wood in a home	NCMA (1976)
Splinter	15,000	"	Sleater and Berger (1977)
Wood wiped by damp human hand	0.529 mg/ft^2	wood 2 yrs old	Dreher (1974)
Treated CCA wood soaked in deionized water	148.32 mg/ft^2	wood soaked for 28 days	Memo (1973)
"	43.2 mg/ft^2	wood soaked for 7 days	"

The Agency assumes that, based on the above data, a homeowner coming into contact with treated wood after flooding would experience the greatest potential exposure. It is conceivable that a home basement could be subjected to flooding for long periods of time. When pressure-treated wood, such as CCA-treated wood, is used in the construction of foundations, a polyethylene film is installed between the soil and the treated wood foundation. The American Wood Preservers Institute (AWPI 1976) says of this polyethylene film, "It should be understood that the polyethylene film serves as a water deflector and is not intended as a water proof membrane. The film will direct ground water downward and away from the wall to the drainage area below. Design of the AWWF (all weather wood foundation) anticipates that the plywood wall may become wet in some cases...."

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For purposes of analyzing potential arsenic exposure resulting from the flooding of home basements constructed of arsenic-treated wood, the following assumptions are made:

1. The basement will be continuously flooded for 7 days;
2. The basement will be 30 feet long, 30 feet wide, and 8 feet high and will be flooded to a depth of 4 feet. This will result in a total of 480 sq. ft. exposed to flood waters;
3. When the flood water recedes 75% of the leached arsenic will be deposited onto the walls or floor;
4. The homeowner will clean the basement after the flood and will require not more than one day to complete the task;
5. 10% of the residual arsenic will come into contact with the skin; and
6. 10% of all arsenic coming into contact with the skin will be absorbed.

Therefore, 480 sq ft (amount of wood subjected to leaching) X 43.2 mg/ft^2 (amount of arsenic leached per sq ft [Memo 1973]) = 20,736 mg leached from wood; 20,736 mg X 0.75 (% of leached arsenic deposited on to walls or floor) = 15,552 mg arsenic; 15,552 mg X 0.1 (% coming in contact with the skin) = 1,555 mg arsenic; 1,555 mg X 0.1 (% absorption) = 155 mg arsenic absorbed. Assuming the person at risk to be a 60-kg woman, exposure would be 155 mg / 60 kg = 2.59

mg/kg resulting from exposure to arsenic-treated wood after flooding.

If flooding were to continue for 28 days exposure would be 8.8 mg/kg.

(ii) Contact with Arsenic-Containing Dust Produced from or by Treated Wood

Table 20 summarizes the relevant data concerning the amount of arsenic available in the dust of homes containing arsenic-treated wood. The Working Group assumes that the homeowner can be dermally exposed with up to 10 grams of dust during the sweeping of arsenic-laden dust, that this dust will contain 1,640 ppm arsenic (Table 20), and that 10% of all arsenic will be absorbed. Therefore, 10 gm of dust X 1.64 mg arsenic/gm of dust (equivalent to 1,640 ppm) = 16.4 mg arsenic coming in contact with the skin. Assuming 10% is absorbed, the homeowner will assimilate 1.64 mg of arsenic. If the resident is a 60-kg woman, the dosage of arsenic would 1.64 mg / 60 kg = 0.03 mg/kg due to dust from arsenic-treated wood.

Total theoretical dermal exposure will be the sum of direct contact with treated wood and contact with dust containing arsenic produced from or by treated wood:

3.45 mg/kg (from flooded basements)

0.03 (contact with dust)

3.48 mg/kg total theoretical dermal exposure.

C. Summary

Table 22 summarizes the available information concerning exposure of a 60-kg woman to arsenic resulting from the use of inorganic arsenical pesticides. The only registered use for sodium pyroarsenate, ammonium arsenite, and arsenic pentoxide is for wood preservation situations; the levels of exposure to these forms of inorganic arsenic are listed under this category. Inorganic arsenical wood preservatives are commonly sold in three formulations (ACA, CCA, and FCAP). Exposure estimates for inorganic arsenical wood preservatives, as detailed in Table 22, were not calculated for each formulation/use situation; however, exposure estimates would be comparable for each use situation.

Human exposure as discussed in this document refers only to exposure resulting from the use of inorganic arsenical pesticides. Other sources of exposure to inorganic arsenic (i.e. smelters, coal-burning plants, volcanic debris) which contribute to the total exposure of the human population have not been discussed. This total exposure to inorganic arsenic would be higher than the exposure from pesticide use alone.

Table 22. Summary of the Total Theoretical Exposure To Inorganic Arsenic Resulting From the Use of Inorganic Arsenical Pesticides

Chemical or Use Situation	Total Theoretical Exposure (for a 60-kg Woman in mg/kg)
Agricultural Situations	
Sodium Arsenite	5.5
Arsenic Acid	2.72
Sodium Arsenate	0.65
Copper Acetoarsenite	0.32
Calcium Arsenate	0.17
Arsenic Trioxide	0.68
Lead Arsenate	0.66
Wood Preservative Situations (Sodium Pyroarsenate (Arsenic Trioxide, Arsenic Pentoxide, Sodium Arsenate, Arsenic Acid, and Ammonium Arsenite)	
Large Industrial Situations	
Inhalation Exposure	0.05
Dermal Exposure	0.57 - 9.0
Intermittent Application to Wood During On-Site Construction	
Dermal Exposure to Ammonium Arsenite	1.1
Exposure From Handling, Sawing, Fabricating, etc, of Treated Wood Products	
Inhalation Exposure	0.27
Dermal Exposure	0.24
Exposure To Individuals Living or Working In Dwellings Containing Arsenic-Treated Wood	
Inhalation Exposure	$7X10^{-7}$ - 0.002
Dermal Exposure	0.03 - 2.59

IV. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

A. Relation Between Arsenate and Arsenite

The inorganic arsenical pesticides discussed previously all have the element arsenic in common. Studies in the following sections describe oncogenic, mutagenic, teratogenic, and other adverse effects of inorganic arsenic salts and/or their metabolites. The Working Group contends that the effect(s) observed are typically due to arsenic from the arsenate or arsenite ions released upon dissociation of the salt in various aqueous systems. The Agency notes that inorganic arsenic salts (i.e. sodium arsenate, sodium arsenite) will, to a greater or lesser extent, dissociate.

40 CFR 162.11(a)(3) provides that "A rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) meet or exceed any of the...criteria for risk." The term "degradation product" is defined by 40 CFR 162.3(1) to mean "a substance resulting from the transformation of a pesticide by physicochemical, or biochemical means," and the term "metabolite" is defined by 40 CFR 162.3(w) to mean "any substance produced in or by living organisms by biological processes and derived from a pesticide." The liberated arsenate and

arsenite ions of the inorganic arsenicals discussed in this document can be considered ingredients of the arsenical pesticides or are encompassed by the 40 CFR definitions of "degradation product" and/or "metabolite."

For purposes of issuing an RPAR, the Agency has made the following determinations:

1. If any form of trivalent inorganic arsenic (arsenite) produces any given chronic effect, it must be assumed that all forms of trivalent inorganic arsenic are capable of producing similar effects, because they all dissociate to the common arsenite ion. This rationale will also prevail for pentavalent inorganic arsenicals (arsenates). The Agency has determined that when a rebuttable presumption is issued for any one pesticide containing arsenate or arsenite, an RPAR will be issued for all pesticides containing arsenate or arsenite, respectively;

2. In addition, as discussed in Section I.J, there is strong evidence that trivalent forms of inorganic arsenic will be oxidized to a pentavalent state in humans, other animals, and the environment. The pentavalent forms of arsenic would be considered degradation products or metabolites (biologically mediated) of trivalent arsenic (arsenites) and, therefore, the trivalent form of arsenic will be subject to regulation based on information from studies on its pentavalent metabolites. The Agency assumes, therefore, that the effects observed in tests using trivalent

arsenites may be due to arsenite, arsenate, or both. The EPA has determined that when an RPAR is issued for any one pesticide containing arsenic in the pentavalent form (arsenate), an RPAR will be issued for all arsenical pesticides containing arsenite, as well as for those containing arsenate; and

3. As discussed in Section I.J, there is also evidence that pentavalent arsenic (arsenate) can be converted to trivalent arsenic *in vivo*. Under these conditions, arsenite would be a metabolite of arsenate and therefore arsenate will be subject to regulation based on information from studies on its trivalent metabolites. The Agency has determined that when an RPAR is issued for any one pesticide containing arsenic in the trivalent form (arsenite), an RPAR will be issued for all arsenical pesticides containing arsenate, as well as for those containing arsenite.

B. Chronic Toxicity

The following adverse effects of inorganic arsenic have been found to exceed the criteria for issuance of a rebuttable presumption.

(1) Oncogenic Effects

40 CFR Section 162.11(a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's

ingredient(s) "(i)nduce(s) oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure...." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce benign or malignant tumor formation in living animals." Epidemiological studies, in conjunction with confirmatory animal tests, provide the best evidence that an agent is a human carcinogen. Albert et al. (1977) noted that "of the chemical agents that are generally accepted to have produced human cancer, all but one [arsenic], produced a carcinogenic response in rats and/or mice...in the same organ as in humans when tested by the appropriate route of exposure." Since arsenic is unique in this respect (Frost 1967; NAS 1977b), the Agency has relied primarily on human epidemiology studies in its assessment of the oncogenicity of inorganic arsenicals.

The information and background data included in the following portion of the position document have been taken from the EPA Carcinogen Assessment Group's Preliminary Report on Inorganic Arsenic (EPA 1978). Studies discussed in this report show that both the trivalent (arsenite) and pentavalent (arsenate) forms of inorganic arsenic act as oncogenic agents. For this reason the

Agency concludes that, without exception, a rebuttable presumption against registration exists for all inorganic arsenical pesticides based on the oncogenic effects criteria. The various forms of inorganic arsenic are enumerated in Section I.A.

Both the National Academy of Science (NAS 1977b) and the Occupational Safety and Health Administration (OSHA 1978) have conducted extensive reviews of the literature concerning the oncogenicity of arsenic. The reader is referred to the NAS and OSHA publications for additional epidemiological studies concerning the oncogenicity of arsenic.

Chronic exposure of humans to inorganic trivalent arsenic from drinking water, medicinal preparations, pesticides, non-ferrous metal smelters, and a gold mine operation has resulted in abnormal pigmentation, keratosis, and skin cancer as well as cancer of the lung and liver in some cases. Chronic exposure of pesticide-manufacturing workers and orchard workers using lead arsenate has resulted in excess incidences of lung cancer. Although concurrent exposure to other chemicals may have contributed to the observed incidence of cancer, the weight of evidence suggests that chronic exposure to either trivalent or pentavalent arsenic can induce cancer. This conclusion is supported by toxicological and mutagenesis studies [see Sections I.J and IV.B.(2)] which show that the two forms of arsenic have similar effects, although trivalent arsenic is more potent than the pentavalent form.

A large body of literature shows that chronic arsenic exposure results in symptoms of abnormal skin pigmentation, keratosis, circulatory disorders leading to gangrene, squamous cell carcinomas, and basal cell epitheliomas of the skin as well as bronchial carcinoma and liver vascular sarcomas (angiosarcomas). These various symptoms result from several exposure situations, summarized below; the valence state of the arsenic compound involved and concomitant exposure to other agents are also considered.

(a) Medical Exposure

Comprehensive reviews by Neubauer (1947), the National Academy of Sciences (NAS 1977b), and Stellman and Kabat (1978) document the occurrence of skin cancer and its early symptoms in patients treated for psoriasis and other conditions with potassium arsenite (Fowler's solution) in the United States before 1950. Since pentavalent arsenic salts are generally not effective therapeutic agents, little information is available concerning their chronic effects from this usage pattern. The evidence indicates that continued administration of potassium arsenite causes circulatory disturbances of the skin, hyperpigmentation, keratosis, skin cancer and, rarely, liver (hepatic) angiosarcoma. Neubauer (1947) found that, in 143 patients with medical skin cancer who had been treated with trivalent arsenic, the latent time between first administration of therapy and the onset of superficial epithelioma ranged between 3 and 40 years, with an average of 18 years. The epitheliomas typically developed on patches of keratotic areas of skin, sometimes after the keratosis had been present for several years; but they also developed on healthy areas of the skin and on patches of psoriasis.

(b) Drinking Water Exposure

Chronic arsenical poisoning, including skin cancer and a gangrenous condition of the hands and feet called Blackfoot's disease, has occurred in several communities exposed to arsenic in drinking water. The best-documented instance of such arsenical poisoning is in Taiwan (Yeh et al. 1968; Yeh 1963; Yeh 1973; Tseng et al. 1968; Tseng 1977). In a house-to-house survey of 40,421 people in 37 villages along the southwest coast of Taiwan, Tseng et al. (1968) found that the prevalence of skin cancer, hyperpigmentation, and keratosis each correlated with the arsenic content of the water. The highest range of concentrations was greater than 0.6 ppm, and the lowest range was less than 0.29 ppm. From a general survey of these inhabitants, the prevalence rate for arsenical skin cancer was 10.6 per 1,000 residents in 1965. The skin cancer rate for well water containing >0.60 ppm was 21.4 per 1,000 people, while at <0.29 ppm it was 2.6.

The sources of drinking water for these areas were deep artesian wells, used from 1910/20 until 1966, when a tap water supply was installed. The concentrations of arsenic in the water ranged from 0.01 to 1.82 ppm (median range was 0.4 ± 0.6 ppm). The chemical form of arsenic in the water was not determined, but it may have been either trivalent (because the well-water is probably anaerobic) or a methylated arsine (because the authors observed a combustible gas [perhaps methane] bubbling from the water storage tanks). Attempts to measure the arsenate to arsenite ratio of the water have been confined to measurements in a United States laboratory of a sample shipped from Taiwan with no special precautions to preserve the speciation occurring at the collection point (Irgolic 1978). The arsenate to arsenite ratio in two samples was 10 to 1 and 7 to 1, with a total arsenic concentration of approximately 0.6 ppm. Since the native water is likely to be anaerobic and since oxidation probably took place to some degree in transit to the analysis laboratory, the ratio in the natural water is probably less than 10 but cannot be assessed at this time. Therefore, from the best available information, people in that region of Taiwan could have been exposed to both trivalent and pentavalent arsenic compounds.

Assessing the Taiwan situation is more complex than simply identifying the two oxidation states of arsenic, as reported recently by Lu et al. (1975, 1977a, 1977b). These workers have observed non-arsenical fluorescent compounds in water samples from the areas where Blackfoot disease is endemic and have identified one of the fluorescent components as an alkaline hydrolysate of ergotamine, lysergic acid, or a related compound (Lu et al. 1977b). They have also shown that one of the fluorescent components produced abnormalities in developing chick embryos (Lu et al. 1977a). It is not known whether ergotamine was the compound that produced these abnormalities.

Two other areas of high levels of arsenic in drinking water are the Cordoba province of Argentina (Bergoglio 1964) and the town of Reichenstein in Selesia (Neubauer 1947). The former is a large farming area with natural geologic deposits of arsenic-containing rock, and the latter is adjacent to a former gold mine with arsenic-containing ores. Skin cancer and other disorders were observed in a large number of people in the areas of Cordoba with high levels of arsenic in the water. The arsenic contamination of ground water in Reichenstein is believed to be responsible for the widespread symptoms in the local population of melanosis and keratotic warts on hands and fingers, perforation of the nasal septum, mouth ulcers, gastrointestinal tract disorders, and skin cancer. The chemical form of arsenic in the drinking water was not stated in these reports.

(c) Exposure in Smelters

Ore containing non-ferrous metals (copper, zinc, and lead) also has high concentrations of arsenic that must be removed in order to produce quality metals. At the smelters producing these metals, arsenic dust is found in the air largely in the form of arsenic trioxide [As_2O_3] (NAS 1977b) or perhaps arsenic sulfides [As_2S_2 or As_2S_3] (Smith et al. 1976). But, as emphasized by Arsenault (1977), the workers are concurrently exposed to sulfur dioxide (Lee and Fraumeni 1969), as well as to sulfates and sulfites (Smith et al. 1976). Occupational studies of smelter workers have been reported in the United States by Pinto and Bennett (1963), Lee and Fraumeni (1969), Milham and Strong (1974), and Pinto et al. (1977), and in Japan by Kuratsune et al. (1974) and Tokudome and Kuratsune (1976). Excess rates of lung cancer among the employees with the highest exposure to arsenic have been found consistently in these studies, although the early Pinto and Bennett study (1963) did not show a significant difference between exposed and control groups. The consistency of these findings in different smelter environments leaves little doubt that arsenic trioxide is at least a major contributor to the incidence of lung cancer in heavily exposed workers. Lee and Fraumeni (1969) have shown that lung cancer rates are also correlated with sulfur dioxide exposure, but there were no populations which had exclusive exposure to either of the agents. Lung cancer mortality among patients in a southern Rhodesian gold mining district has been studied by Osburn (1969). He found that of 37 people who died over 15 years, 13 also had hyperkeratosis characteristic of chronic arsenical poisoning. All but one patient had known exposure to dust containing arsenic from the mines.

(d) Exposure to Inorganic Arsenical Pesticides

Both trivalent and pentavalent arsenic are used in pesticide products. Reports of skin, lung, and liver cancer in people exposed during the manufacture and use of these compounds have been published. In manufacturing plants an excess of respiratory cancer was reported by Ott et al. (1974), Ott (1976), and Hill and Faning (1948). The use of inorganic arsenical pesticides has been associated with cancer of several organs in German and French vintner workers by Roth (1956, 1957a, 1957b, 1957c, 1958), Denk et al. (1969), Thiers et al. (1967), Braun (1958), von Pein (1943), Galey et al. (1963), and Petres and Hagedorn (1975).

(i) Exposure in Pesticide Manufacturing Plants

A study of factory workers in the Dow Chemical Company's pesticide manufacturing plant (Ott et al. 1974) showed excess rates of respiratory and lymphatic cancer. The authors found that the rate of respiratory cancer correlated with the inorganic arsenic exposure level. Although there was minor exposure in a building where the arsenic trioxide starting material was loaded into the equipment, the workers were predominantly exposed through bagging to finished calcium and lead arsenate products. Production of arsenic compounds over the entire 37 years of operation was estimated to be 59% lead arsenate, 34% calcium arsenate, 5% copper acetoarsenite, and 2% magnesium arsenate.

These effects can therefore be ascribed to pentavalent, rather than to trivalent arsenic. Exposure to powdered sulfur and dry lime sulfur also occurred (Ott et al. 1974).

In a British factory manufacturing a sodium arsenite sheep dip compound, Hill and Faning (1948) observed a high rate of lung and skin cancer among workers directly handling the compound.

(ii) Exposure via Use of Pesticides

Inorganic arsenic pesticides were used on grapes in France and Germany between the early 1920s and 1942. Roth (1957b) reported the occurrence of chronic arsenical poisoning, including sequelae of skin and lung cancer, in French and German vintners. (These same sequelae of skin and lung cancer have also been observed in patients medicinally treated with inorganic arsenic.) In addition, a rare form of liver cancer, hemangio-endothelioma, was observed in the vintners. The most complete description of the cases is in a series of papers by Roth concerning the Mosel River Valley wine-growing area, but chronic arsenical poisoning also occurred in the upper Baden Valley, where it was called the "Kaiserstuhl Sickness" (Petres and Hagedorn 1975), and in the Rhine, Pfalz, and Wachau regions in Germany and the Beaujolais region in France (Galey et al. 1963; Thiers et al. 1967).

As Roth (1958) points out, not all wine-growing regions in Germany used inorganic arsenical insecticides because the particularly voracious insect that was susceptible to arsenic poisoning was not present everywhere. This insect is *Cochylis* (or *Clysia*) *ambiguella*, also known as the hay worm and sour worm (Thiers et al. 1967; Stellwaag 1928). It has two generations per growing season. The first caterpillars appear in June when the hay is harvested, and the second generation appears in late summer. A detailed description of these insects is given by van Emden (1936).

A dust of calcium arsenate, applied every two weeks in early summer, was particularly effective against hay and sour worms (Stellwaag 1928). This mixture contained calcium and As_2O_5 (pentavalent arsenic) with an arsenic concentration of 10 to 15%, and was called Sturm's Dusting Material by some (Frohn 1938). This technique was not popular for long because of the extremely acute reaction of the vintners to the dust, but it was used in cases of severe infestation. Another arsenic preparation, applied as a spray, was a mixture of copper acetoarsenite (or paris green), also known by the trade names of "Selesia Green" and "Urania Green," which is a copper-lime solution (Stellwaag 1936). The copper-lime solution alone controls the common fungus

Peronspora, and the combination spray (including paris green) is effective against both the fungus and the hay and sour worms. The vintners were therefore exposed to both trivalent arsenic, as copper acetoarsenite, and pentavalent arsenic, as calcium arsenate, during the growing season.

A second, and perhaps major, source of vintner exposure to inorganic arsenic was by drinking the "house wine," prepared from the second pressing of grape skins. Stellwaag (1928) states that, during the fermentation process, a large fraction of the arsenic was removed from the liquid by transformation into arsenic sulfide, which was subsequently absorbed by the yeast. This form of arsenic should, therefore, appear in the "house drink," which was consumed in quantities of 1 to 3 liters per day during the warm season. Crecelius (1977a) has shown that, during the fermenting of grape juice, the final ratio of trivalent to pentavalent arsenic was about 4 to 1, regardless of whether the starting material was all trivalent or all pentavalent, and that the fermenting process tends to convert arsenic of both valences predominantly to the trivalent form.

In summary, the inorganic arsenic responsible for the chronic poisoning and cancer in the vintners was a complicated mixture of pentavalent and trivalent compounds, perhaps combined with sulfur.

The Wenatchee Valley in central Washington is another site where arsenical pesticides have been used for many years in the form of lead arsenate in apple orchards. Nelson et al. (1973) found no excess rate of lung cancer in orchardists, but the National Institutes of Occupational Safety and Health (NIOSH 1975) recently re-examined the mortality statistics in the state of Washington and found a statistically significant increase of respiratory cancer.

An epidemiological study of carpenters in Hawaii, who were exposed to pentavalent arsenic wood preservatives for an unknown period of time, was published by Budy and Rashad (1976). The rate of respiratory cancer among carpenters who died between 1970 and 1973, as compared to matched non-carpenter control groups, was not significantly different than the corresponding rate for those who died between 1948 and 1951. In the earlier years, about 5% of the wood was treated with arsenic, whereas in the early 1970s about 50% of the wood was so treated. Uncertainty about the degree and duration of exposure makes this study difficult to interpret.

(e) Summary of Human Exposure Studies

Chronic exposure of humans to sufficiently high doses of arsenic in several situations has produced abnormal pigmentation, keratosis, and skin cancer as well as cancer of lungs, liver, and perhaps other sites. The adverse effects resulting from this exposure have been consistently the same as those produced by medicinal use of potassium arsenite; and, with two exceptions, the exposures have all involved trivalent arsenic. Therefore, it is extremely likely that trivalent arsenic is a human oncogen. Two situations of arsenic exposure, in which the predominant form of arsenic is pentavalent, have produced lung cancer; these are the Dow pesticides manufacturing plant and the lead arsenate exposures in Wenatchee, Washington. Although it is difficult to rule out other chemicals as the causative agents, these two situations furnish ample cause for concern that pentavalent arsenic may also be oncogenic.

(f) In Vitro Studies Suggestive of Oncogenic Potential

Although *in vivo* animal studies have not yet confirmed inorganic arsenic to be oncogenic, several positive *in vitro* cell transformation studies have been published. For certain cell lines, *in vitro* transformation from primary (normal, diploid) cells to cancerous ones is a good indicator of the carcinogenic potential of a compound. The best validated test systems are the Syrian hamster embryo cell system of Dr. R. Pienta (NCI) and the Chinese hamster ovary cell system used by Dr. DiPaolo (NCI).

These are short-term testing systems for oncogenicity and produce few, if any, false positives.

Casto et al. (1976) showed that sodium arsenite induced the transformation of Syrian hamster fetal cells that were seeded to form colonies. Arsenite also enhanced the frequency of simian adenovirus (SA7) transformed foci. Spontaneous transformations were not observed in the controls. The increase in SA7 transformation frequency was not due to selective toxicity, since there was a 2- to 3-fold increase in treated cultures in the number of foci per plate.

Casto (Letter 1977a) elaborated on this work (described above) with data that supported the conclusion of *in vitro* transformation of these hamster embryo cells by sodium arsenite. At a concentration of 1.2 ug/ml, transformation was enhanced 2.4 times over the background level (significant at 5% level). The responses were dose-related.

Casto et al. (1977) assayed Syrian hamster embryo cells for enhancement of viral transformation by an inorganic salt of arsenic (sodium arsenite). Hamster cells were exposed to arsenic either 18 hours before or 5 hours after the addition of simian adenovirus (SA7). Survival was determined by cloning methods, and viral transformation was detected by focus assay. There was a significant increase in the relative transformation frequency and in the absolute number of SA7 foci per plate. This indicates the increase was not due to selective toxicity. Enhancement occurred at concentrations that did not affect cloning efficiency.

Moore (1976) used Fischer rat embryo cells infected with Rauscher leukemia virus and a cloned cell line of mouse BALB/3T# to assay for _in vitro_ cell transformation by arsenic trioxide. A positive control (3-methylcholanthrene) was used. The results for the rat and mouse cell systems were negative. The Fischer rat embyro system is not validated.

(g) Conclusion

EPA concludes that sufficient epidemiological data exists to show that both trivalent inorganic arsenic (arsenite) and pentavalent inorganic arsenic (arsenate) act as oncogenic agents in humans. This position is in agreement with that of the Occupational Safety and Health Administration (OSHA 1978) who conclude "(t)hat there is virtually no dispute as to the carcinogenicity of trivalent arsenic," and that, on the basis of the available evidence, "pentavalent arsenic should be regulated as a human carcinogen." Section I.J presents strong evidence of the ability of inorganic arsenic to interconvert _in vivo_ (arsenite to arsenate and arsenate to arsenite). As discussed in Section I.J, this interconversion makes trivalent arsenic a metabolite of pentavalent arsenic and pentavalent arsenic a metabolite of trivalent arsenic.

Therefore, in the case of pentavalent inorganic arsenic, the Agency stresses that the RPAR is being issued for two reasons: 1) that pentavalent arsenic is an oncogen and 2) that pentavalent arsenic is reduced in vivo to trivalent arsenic, which also acts as an oncogen. The Agency concludes that either characteristic of pentavalent arsenic is sufficient criterion for the issuance of an RPAR.

The basis for issuance of an RPAR for trivalent inorganic arsenic is similar: 1) that trivalent arsenic is an oncogen and 2) that trivalent arsenic is oxidized in vivo to pentavalent arsenic, which also acts as an oncogen.

(2) Mutagenic Effects

40 CFR Section 162.11(a)(3)(ii)(A) provides that "A rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) ...induces mutagenic effects, as determined by multi-test evidence."

Studies discussed in this report (and summarized in Table 23) show that both trivalent (arsenite) and pentavalent (arsenate) forms of inorganic arsenic can act as mutagenic agents. The EPA concludes that these studies represent multi-test evidence and that, without exception,

Table 23. Summary of Studies of Inorganic Arsenic Mutagenicity.

Study	Author(s)	Chemical(s)	Cell Type	Effects
1. Point Mutation	Ficsor and Lo Piccolo 1972	sodium arsenate	*E. coli*	No reversions induced
	Moore 1976	arsenic trioxide	*S. typhimurium*	Negative Ames' test (without metabolic activation)
	Nishioka 1975	sodium arsenite	*E. coli*	Positive mutagen (induced tryptophan reversions).
	Casto (Letter 1977a)	sodium arsenite	hamster lung cells	Positive mutagen - increased the frequency of mutation in 8-azaguanine treated cells.
2. Chromosomal Effects *In vitro* Cytogenetics	Oppenheim and Fishbein 1965	potassium arsenite	human peripheral leukocytes	Chromosome gaps, breaks, translocations, dicentrics, ring forms were found. Cell division was supressed and there was an increased number of broken metaphase plates.
	Paton and Allison 1972	sodium arsenite	human diploid fibroblasts	Chromatid breakage
		sodium arsenite sodium arsenate	human diploid fibroblasts and leukocytes	Chromatid breakage > Effect higher with sodium arsenite Chromatid breakage > Effect higher with sodium arsenite
In vivo Cytogenetics	Petres et al. 1976, 1977	unspecified	human lymphocytes (from psoriasis patients and wine-growers)	Aneuploidy, chromatid breaks, acentric fragments, and dicentric chromosomes occurred more frequently in cells from persons exposed to arsenic than in the controls.
Dominant Lethal Effects	Sram and Bencko 1974	sodium arsenite	ICR-SP mice	An acute oral dose (250 mg/kg) given to the male produced negative results. Chronic application over 4 generations of males at 10 mg/liter of drinking water gave positive results (increase in overall dominant and preimplantation lethality). A subtoxic dose (100 mg/liter) gave no change in frequency of dominant lethality or male fertility.

3. DNA Damage	Burgdorf et al. 1977	potassium arsenite	human lymphocytes	There was a higher rate of sister chromatid exchange in lymphocytes from patients who had used Fowler's solution compared to lymphocytes from unexposed controls.
4. DNA Repair (microbial)	Rossman et al. 1975, 1977	sodium arsenite	*E. coli* (uv-exposed)	There was decreased mutation frequency of irradiated cells that were excision-repair deficient. There was decreased survival rate of uv-exposed cells (wild type, excision-repair deficient). No effect was found on strain deficient in post - replication repair.
	Nishioka 1975	sodium arsenate sodium arsenite	*Bacilus subtilis*	Both chemicals were positive mutagens. The effect was stronger with sodium arsenite.
(mammalian)	Jung et al. 1969	sodium arsenate	human epidermal cells (exposed to xenon lamp)	DNA dark repair activity decreased in presence of sodium arsenate.
	Jung and Trachsel 1970	sodium arsenate	human epidermal cells (exposed to xenon lamp)	DNA synthesis (reduced mitotic index) and DNA dark repair were both inhibited in presence of sodium arsenate.
5. Metabolic and Cellular Toxicity Effects				
(*in vivo*)	Skipper et al. 1951	potassium arsenite	mice	There was reduced incorporation of ^{14}C-formate (precursor of mouse DNA-purines) into nucleic acid purines.
	Sawada and Rebhun 1969	sodium arsenite	annelid worm eggs	There was inhibition of the formation of the mitotic apparatus (before fertilization).

(in vitro)	Tsuda 1974	sodium arsenate	mouse fibroblasts	The indices for prophase, metaphase, and mitosis increased, but decreased for telophase.
	Petres and Hundeiker 1968	sodium arsenate	human peripheral lymphocytes	The number of mitoses was reduced to 1/5 the expected number. Chromosome pulverization occurred consistently.
	Petres and Berger 1972	sodium arsenate	same	At high concentrations, the mitotic index decreased. There were metaphase plate pulverizations at low doses. There was inhibition of ^{3}H-thymidine incorporation into DNA.
	Petres et al. 1974	sodium arsenate	same	There was inhibition of ^{3}H-thymidine and ^{14}C-thymidine incorporation into DNA at lower doses than inhibition of ^{3}H-uridine and ^{14}C-uridine into RNA.
	Petres et al. 1975	sodium arsenate	same	After one hour of exposure, there was increasing inhibition of ^{14}C-thymidine incorporation into DNA.
	Baron et al. 1975	sodium arsenate	same	There was inhibition of ^{14}C-TTP into DNA and ^{14}C-UTP RNA. There was also inhibition of incorporation of labeled alanine and leucine into cellular proteins.

a rebuttable presumption against registration exists for all inorganic arsenical pesticides based on the mutagenic effects criterion. The various forms of inorganic arsenic are enumerated in Section I.A.

(a) Studies Relevant to Rebuttable Presumption

(i) Point Mutation Studies

Nishioka (1975) examined the mutagenic effect of sodium arsenite on strains of *E. coli* by reversion studies. The *E. coli* strains used were WP_2 (trp^-, $uvrA^+$, $recA^-$); WP_2 uvrA (trp^-, $uvrA^-$, $recA^+$); and CM_{571} (trp^-, $uvrA^+$, $recA^-$). These strains were exposed to sodium arsenite concentrations ranging from 1.6×10^{-4} to 8.0×10^{-4} M. Reversions were induced in all but the CM_{571} strain of *E. coli*.

Casto (Letter 1977a) demonstrated that sodium arsenite was a point mutagen. Chinese hamster lung diploid cells (*Cricetulus griseus*, DCN line) were grown in THAG medium. Sodium arsenite was added to the culture for 18 hours and then removed by adding fresh plain medium. After a 48-hour expression time, 10 ug/ml of 8-azaguanine was added. The culture medium was replaced with fresh medium containing 8-azaguanine every 48 hours for 20 to 25 days of incubation. For mutation assays the cells were fixed and stained. The cells for survival assays were grown in medium with the arsenic and then placed in plain medium. The cells were later fixed and stained and surviving colonies were counted.

The frequency of mutation was expressed as the number of 8-azaguanine resistant colonies per 10^6 surviving cells. The spontaneous mutation frequency of this cell line was less than 1 mutant per 10^6 surviving cells. Without sodium arsenite, there were 0.45 8-azaguanine resistant colonies per $5x10^5$ cells (mutation frequency of 0.9 colonies per 10^6 surviving cells). At 5 ug/ml of sodium arsenite, there were 9.6 resistant colonies per $5x10^5$ cells (mutation frequency of 65.0 mutant colonies per 10^6 surviving cells).

Fiscor and Lo Piccolo (1972) tested an ant poison, containing 3% sodium arsenate, for mutagenicity by bacterial-plate assay. The compound (dosage not given) was tested for its ability to revert two E. coli lac^- amber mutants (NG 422, YA 482) to the lactose-fermenting phenotype, and to revert a cys^- (cysB12) and two leu^- (AP517, 5BU504) auxotrophs to prototrophy. All five strains had a low frequency of spontaneous reversions, and each was reversible by the positive control (known mutagen) N-methyl-N'-nitro-N-nitrosoguanidine. The results were negative.

Moore (1976) used the Ames' test, without metabolic activation, to test the mutagenicity of arsenic trioxide on 5 (or 4) strains of *S. typhimurium*. Positive controls (4-nitroquinoline-N-oxide and N-methyl-N'-nitrosoquanidine) were used. The results were negative for arsenic trioxide.

(ii) Bacterial DNA Repair

Nishioka (1975) examined the mutagenic effect of sodium arsenate and sodium arsenite on strains of *Bacillus subtilis* by rec-assay. For the assay, a 0.05 ml aliquot of either arsenic compound (at a concentration of 0.05 M) was dropped on filter paper which was placed on plates containing *B. subtilis* strains H_{17} (rec^{+}, arg^{-}, trp^{-}) or M_{45} (rec^{-}, arg^{-}, trp^{-}). Sodium arsenate was a positive mutagen, but its effect was less distinct than the effect with sodium arsenite.

(iii) Chromosomal Aberration Studies

1. In Vitro Cytogenetics

Oppenheim and Fishbein (1965) cultured human peripheral leukocytes stimulated with phytohemagglutinin (stimulates mitotic activity) for 72 hours in 0.5, 1.0, 3.3, and 10.0 uM potassium arsenite solutions (arsenic trioxide in dilute potassium bicarbonate). An additional culture was treated for 48 hours in a solution of 1.0 uM concentration. At a concentration of 1 uM, potassium arsenite induced chromosomal damage, such as chromosome gaps and breaks, translocations, dicentrics, and ring forms. Potassium arsenite also supressed cell division, increased the number of broken metaphase plates, and increased cell damage at the higher concentrations. These effects increased from the 48-hour to the 72-hour treatment, with the exception of cell division which was suppressed more at 48 hours.

Paton and Allison (1972) investigated the effects of subtoxic doses of sodium arsenite and sodium arsenate on cultured human diploid fibroblasts and leukocytes. In chromosomal studies, leucocyte cultures were treated for 48 hours with 2.9×10^{-9} to 1.8×10^{-8} M solutions of sodium arsenite or 5.8×10^{-9} M sodium arsenate. Of the metaphase plates examined, 60% (sodium arsenite) and 5% (sodium arsenate) of the cells had chromatid breakage. In fibroblast cultures treated for the last 24 hours of culture with 2.9×10^{-9} to 5.8×10^{-8} M sodium arsenite, 20% of the metaphase plates showed chromatid breakage. These values were significantly higher ($p = 0.01$) than the control values for leukocytes (2%) and for fibroblasts (3%).

To study long-term effects, cultured fibroblasts and leukocytes were treated for several weeks with subtoxic doses of these arsenic salts. The cells were often over-contracted but otherwise did not differ from the control cells. In short-term exposure (24 to 48 hours) of fibroblast and leukocyte cultures to sodium arsenite and sodium arsenate, there was significantly more chromatid breakage than in the control cultures. The breaks were often located close to the end of a chromosome. The incidence of chromatid exchange was higher in leukocytes than in fibroblasts.

2. In Vivo Cytogenetics

Petres et al. (1970; 1977) did chromosomal analyses of lymphocytes from a group of patients previously exposed to arsenic and from a control group with no previous exposure to arsenic. Since the 1977 study appears to include many of the same persons in the first study, only the latter paper will be discussed. The control group consisted of 14 psoriasis patients and 17 healthy patients, both without a history of exposure to arsenic. The test group included 14 psoriasis patients medically treated with arsenic and 17 vineyard workers who had used arsenical pesticides. In some cases the last exposure to arsenic occurred more than 30 years previously. The control group averaged 14 years younger than the exposed patients. The male/female sex ratio was near unity in the control group but was approximately 6/1 for the exposed group. All patients who had been exposed to arsenic had palmar and plantar hyperkeratosis and some history of cutaneous carcinomas.

Several observations were made on cultured lymphocytes:

1. Chromatid breaks, acentric fragments, and dicentric chromosomes occurred more frequently in cells from persons exposed to arsenic (76/1121=0.07) than in control cells (3/1247=0.002) ($p<0.001$). Two dicentric chromosome-containing cells were found in treated persons; none were noted in controls. No information was given as to the distribution of the aberrant cells among the subjects;

2. Aneuploidy occurred significantly more frequently in cells from treated subjects than in cells from controls (26.7 and 7.1% of the treated and control cells, respectively). It is not known if the aberrant cells were distributed randomly among subjects. The high frequency of aneuploid cells in exposed persons is difficult to interpret, because essentially all aberrant cells were hypodiploid; cells with hyperdiploid chromosome numbers were not found; and

3. The incorporation of radioactively-labeled thymidine and uridine into DNA and RNA decreased in a dose-response fashion in cultures of lymphocytes, from control persons, treated with exogenous sodium arsenate (0.05 to 100 ug/ml). The effect of arsenate on nucleotide transport into cells and on thymidine/uridine phosphorylation to nucleotides for incorporation into nucleic acids was not assessed.

3. Dominant Lethal Effects

Using sodium arsenite, Sram and Bencko (1974) performed a dominant lethal test with ICR-SPF mice using both acute and chronic multi-generation dosing regimens, and tested for synergistic effects with TEPA, a positive control mutagen. To determine if sodium arsenite can induce dominant lethal mutations, a toxic dose of 250 mg/kg was applied perorally (acute test). The results were negative.

In a second study of chronic application over four generations, weaned male mice were given either 10 or 100 mg of arsenic per liter of drinking water ad libitum over an 8-week period. Based on consumption of water, the actual intake of arsenic was 1.6 mg/kg per day (10 mg/liter) and 9 to 10 mg/kg per day (100 mg/liter). During each of the eight weeks, several male mice (P_1) were mated, and the next three generations came from these matings. In males given 10 mg/liter, the overall dominant lethality and preimplantation lethality increased in the second and third weeks of mating. In other weeks there was no difference from the controls. The males exposed to 100 mg/liter (subtoxic) showed no change in the frequency of dominant lethal mutations or male fertility.

A third study of synergistic effects with TEPA (reference chemical mutagen) was done. A single intraperitoneal dose of 1 mg of TEPA per kg was given to males of the F_3 generation that were given either 10 or 100 mg/liter of sodium arsenite. For treatment with TEPA and 10 mg/liter of arsenic, there was no increase in the number of mutagenic effects over that seen with 1 mg of TEPA. At 100 mg/liter of sodium arsenite and TEPA, there was an increase in the overall dominant and preimplantation lethality which increased significantly in the second week.

(iv) DNA Damage

Burgdorf et al. (1977) found an elevated sister chromatid exchange rate (SCE) in lymphocytes from six patients who had used Fowler's solution (containing potassium arsenite) compared to lymphocytes from 44 unexposed controls. The lymphocytes were cultured in total darkness with phytohemagglutinin, penicillin-streptomycin, and bromodeoxy uridine and treated with colchicine for three hours. The cells were fixed and stained for SCE. Centromeric exchanges were differentially included in the total SCE counts.

The arsenic-exposed patients had a mean of 14.00 SCE/mitosis with a range of 4 to 30 (standard deviation, 3.12). The controls had a mean of 5.8 SCE/mitosis with a range of 1 to 23 (standard deviation, 2.27). There was no difference in chromosomal breakage between the two groups.

(v) DNA Repair Studies

Rossman et al. (1975) irradiated strains of *E. coli*, differing only in repair markers, with UV light and exposed the cells to various concentrations of sodium arsenite. Culture samples were irradiated in petri dishes with a 15 W germicidal lamp at a distance of 50 cm. After exposure, serial dilutions were made and plated onto nutrient agar containing the following concentrations of sodium arsenite: 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} M.

The wild type (WP2) and excision-repair deficient strains WP6 and WWP2 (polA^{-} and uvrA^{-}, respectively) showed decreased survival in the presence of 0.1 mM of sodium arsenite. The magnitude of the effect increased with increasing UV doses. There was no apparent effect on survival of the unirradiated cultures of WP2, but there was a loss of colony-forming ability at a concentration of 5 mM. Sodium arsenite had no effect on the survival of WP10 cells (recA^{-}, deficient in post-replication repair) at any dose. The survival of WP5 cells (lex^{-}) was increased significantly (statistical significance not given) by sodium arsenite, and the effect decreased with increasing UV doses. The authors postulated that arsenite inhibits a recA^{-} dependent step in DNA repair. For increased survival of the lex^{-} mutant, WP5, it is suggested that in the absence of the lex^{+} gene, the arsenite-sensitive recA-dependent function is deleterious.

Rossman et al. (1977), based on the findings in their first paper, attempt to support their hypothesis that arsenicals inhibit some aspect of DNA repair, specifically that sodium arsenite affects post-replication repair.

Strains of *E. coli* differing only in repair markers were irradiated with UV light and then plated onto medium containing 0.1 mM sodium arsenite. The strains used were:

WP2 (wild type for repair); WP6 and WWP2, both excision-repair deficient; WP10, deficient in post-replication repair; and WP5. Compared to control cultures, sodium arsenite decreased the survival rate of UV-exposed cells of strains WP2, WWP2, and WP6. There was no effect on survival of strain WP10, and survival increased in strain WP5. Sodium arsenite also had no effect on cultures that were not irradiated.

The excision-repair deficient strain WWP2 is more subject to mutation than the wild type WP2. The mutation frequency for this strain was measured after exposure to UV light, by scoring for trp^+ revertants. Cultures were exposed to UV light and plated with 1 mM sodium arsenite. Controls at each UV dose level were plated onto plain nutrient agar. Sodium arsenite decreased the absolute mutation frequency and the number of mutations per survivor at all UV exposures. At higher UV levels, survival of the cells dropped below 1%.

Based on their data, the authors speculated that sodium arsenite inhibits post-replication repair of DNA by inhibiting a recA-dependent function such as SOS repair. This DNA repair pathway is inducible in damaged cells (i.e., by UV exposure), repressed in undamaged cells, and is error-prone. After UV exposure, sodium arsenite decreased mutagenesis in strains WP2, WWP2, and WP6 containing the $recA^+$ and lex^+ genes (upon which mutagenesis depends).

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The effect of sodium arsenite (inhibition of post-replication repair) on the survival of UV-irradiated strains of E. coli increased with increasing irradiation. The authors believe this supports their hypothesis that post-replication repair is inhibited by sodium arsenite. This becomes more important at higher UV doses due to saturation of the excision repair capacity.

When Jung et al. (1969) exposed human epidermal cells to sodium arsenate, there was a temporary reduction in enzymatic dark repair activity of DNA. Dark repair is the non-light dependent cell repair mechanism consisting of several enzymatic steps by which single-strand DNA lesions can be recognized, excised, and repaired.

Skin grafts from human male subjects were incubated for either one or four hours in medium containing either 10^{-5} or 10^{-6} M sodium arsenate. The cultures were then irradiated with an unfiltered xenon lamp and incubated with ^{3}H-methyl thymidine for four hours. In the stratum basale, stratum spinosum, and stratum granulosum, the thymidine labeling was visible in many nuclei as "light marking", which is regarded as repair marking and is dependent on the intensity of irradiation. A statistical evaluation showed that repair activity fell significantly ($p<0.05$) as a result of incubation with sodium arsenate. There was no statistically confirmed difference between the incubation periods of one and four hours or between arsenic concentrations of 10^{-5} and 10^{-6} M.

Jung and Trachsel (1970) showed that sodium arsenate inhibited DNA synthesis and DNA dark repair in human epidermal cells. The cells were cultured in medium containing 10^{-5} or 10^{-6} M sodium arsenate for one or four hours. The cultures were then radiated with an unfiltered xenon lamp. Radio-labeled thymidine was added to the cells which were then incubated for four hours. The cells were fixed, stained, and autoradiographed. The number of premitotic "marked" cells per 1,000 cells was calculated and used as the mitotic index.

Cells from various stages of the incubation process were examined: control cells, cells irradiated only, cells incubated with sodium arsenate (1 hour), and cells irradiated and cultured with sodium arsenate. Radiation and arsenic alone reduced the mitotic index, but this effect was significantly greater with simultaneous exposure ($a = 0.01$).

To measure the effectiveness of the dark repair system, the number of silver grains per cell surface was measured for 200 epidermal cells (measure of thymidine incorporation into DNA). There was a statistically significant ($a = 0.05$) reduction in dark repair due to sodium arsenate. There was no difference between a 1- or 4-hour incubation time or between 10^{-5} and 10^{-6} M concentrations of arsenate.

The Agency concludes that there is multi-test evidence for the mutagenicity of inorganic arsenates and arsenites. Based on Nishioka (1975), there is evidence that both arsenate and arsenite compounds are positive point mutagens. In studies by Jung et al. (1969) and Rossman et al. (1977), inorganic arsenate and arsenite inhibited DNA repair mechanisms. Both in vitro and in vivo studies show that arsenite and arsenate induced chromosomal aberrations in various cultured human cells and in lymphocytes taken from psoriasis patients and vintners.

The Agency concludes, therefore, that sufficient data exist on the mutagenicity of both trivalent inorganic arsenic (arsenite) and pentavalent inorganic arsenic (arsenate). Section I.J presents strong evidence of the ability of inorganic arsenic to interconvert in vivo (arsenite to arsenate, and arsenate to arsenite). As discussed in Section III.A, this interconversion makes trivalent arsenic a metabolite of pentavalent arsenic, and pentavalent arsenic a metabolite of trivalent arsenic.

Therefore, in the case of pentavalent inorganic arsenic, the Agency stresses that the RPAR is being issued for two reasons: 1) that pentavalent arsenic is a mutagen and 2) that pentavalent arsenic is reduced in vivo to trivalent arsenic, which also acts as a mutagen. The EPA concludes that either characteristic is a sufficient criterion for the issuance of an RPAR.

The basis for issuance of an RPAR for trivalent inorganic arsenic is similar: 1) that trivalent arsenic is a mutagen and 2) that trivalent arsenic is oxidized in vivo to pentavalent arsenic, which also acts as a mutagen.

(b) Studies on Which Further Information is Sought: Metabolic and Cellular Toxicity Effects

This section addresses effects of inorganic arsenicals on genetic material and processes that are probably due to metabolic and cellular toxicity, but for which insufficient evidence exists to initiate a rebuttable presumption. The Agency requests registrants or other interested persons, having information on these effects, to submit such data to the Agency. The following studies indicate that inorganic arsenicals affect the mitotic process and induce chromosomal pulverization as well as inhibition of the incorporation of important precursors into DNA and RNA.

Skipper et al. (1951) injected CFW strain mice intraperitoneally with an 18.0 mg/kg dose of potassium arsenite. This was immediately followed by an injection of ^{14}C-sodium formate. The control mice received only the injection of labeled sodium formate. After six hours, all groups of mice were sacrificed. Potassium arsenite markedly reduced the incorporation of ^{14}C-formate into nucleic acid purines. In the rat, formate carbon is a required precursor of the bases in deoxyribonucleic acid (guanine, adenine, and thymidine) and of ribonucleic acid (guanine and adenine).

Sawada and Rebhun (1969) studied the effects of sodium arsenite on eggs of the annelid worm *Pectinaria gouldi* which develop the first mitotic apparatus (MA) after they are shed into sea water. The MA will remain at metaphase for several hours until the egg is fertilized. Prior to the formation of the MA, eggs were immersed in solutions of sodium arsenite in sea water (concentration not specified). This completely inhibited the formation of the MA in annelid worm eggs. If development of the MA was allowed to occur, the minimum concentration for its dispersion was 5 x 10^{-3} M This dispersion was irreversible.

Petres and Hundeiker (1968) cultured phytohemagglutinin-stimulated human lymphocytes of peripheral blood from nonarsenic-exposed donors for 72 hours. At either 24 or 48 hours before terminating the cultures, sodium arsenate was added at the concentrations of 10^{-6} and 5 x 10^{-6} g/ml of culture media. Control cultures were prepared without sodium arsenate. Compared to the controls, the number of mitoses in the cells treated with sodium arsenate was reduced to approximately one fifth (1/5) the expected number. Chromosome pulverization occurred consistently in cultures incubated for 24 or 48 hours with sodium arsenate.

Petres and Berger (1972) studied the potential cytotoxic and mutagenic effects of sodium arsenate tested *in vitro* on cultured human lymphocyte cells of peripheral venous blood from non-arsenic-exposed donors. The cells were cultured for 72 hours in a medium containing phytohemagglutinin. Forty-eight hours before termination of the cultures, sodium arsenate was added at the following concentrations: 3×10^{-5}, 1×10^{-5}, 5×10^{-6}, 2×10^{-6}, 1×10^{-6}, 5×10^{-7}, 1×10^{-7}, and 5×10^{-8} g/ml of culture medium. Control cultures were grown without sodium arsenate. ^{3}H-thymidine was also added to both test and control cultures. The mitotic index decreased considerably only with the higher sodium arsenate solutions. Serious nuclear division disorders and metaphase plate pulverization occurred at low doses. At the concentrations of 1×10^{-7} and 2×10^{-6} g/ml, there were 36.3% and 80 to 100% pulverizations, respectively. The ^{3}H-thymidine labeling index was significantly reduced at the mid-level doses compared to the control values. This reduction in the index indicates inhibition of ^{3}H-thymidine incorporation into DNA.

Petres et al. (1974) added sodium arsenate to cultures of phytohemagglutinin-stimulated human lymphocytes of peripheral venous blood from non-arsenic-exposed donors. The incorporation of radioactively labeled thymidine and uridine into DNA and RNA was measured by scintillation counting and autoradiography. Sodium arsenate was added 24 hours before termination of the 72-hour incubation period at the following concentrations (ug per ml of medium): 0.05, 0.1, 0.5 (thymidine only), 1.0, 2.0 (thymidine only), 5.0, 10.0, 30.0, 50.0, and 100.0. Control cultures were simultaneously prepared without sodium arsenate. Six hours before termination of the cultures, either H-^{3}thymidine or H-^{3} uridine was added to one set of the cultures.

For scintillation counting, cultures were prepared with sodium arsenate concentrations of 0.05, 0.1, 10.0, 30.0, 50.0, and 100.0 ug of sodium arsenate per ml of culture medium. Controls without sodium arsenate were also prepared. Eighteen hours before termination of the 72-hour culture period, either ^{14}C-thymidine or ^{14}C-uridine was added to a culture.

The marker index obtained using autoradiography indicated that inhibition of ^{3}H-thymidine incorporation into DNA began at low concentrations of sodium arsenate (i.e., 0.1 ug/ml). This inhibition increased with increasing concentrations, and at 100 ug/ml there was 97% inhibition compared to controls. Inhibition of ^{3}H-uridine incorporation into DNA began at concentrations of sodium arsenate greater than 10 ug/ml. At 100 ug/ml there was 50% inhibition compared to controls.

Using scintillation counting, inhibition of ^{14}C-thymidine incorporation into DNA was detected at 1.0 ug/ml and increased with higher concentrations. Inhibition of ^{14}C-uridine incorporation into RNA was detected at concentrations greater than 10.0 ug/ml.

Petres et al. (1975) cultured phytohemagglutinin-stimulated human lymphoctes of peripheral blood from non-arsenic-exposed donors for 72 hours. From 1 to 18 hours before termination of the cultures, either 10, 30, or 50 ug of sodium arsenate was added per ml of culture medium. Parallel control cultures were prepared without sodium arsenate. Later ^{14}C-thymidine was added to each culture. In human lymphocyte cultures exposed to various levels of sodium arsenate for one hour, there was a 17% increase in the incorporation of ^{14}C-thymidine into DNA. As the exposure time increased, there was a general decrease in the incorporation rate. After 18 hours of incubation with 10 ug of sodium arsenate, the incorporation rate was inhibited up to 35%. At the higher concentrations, there was 65 to 70% inhibition.

Baron et al. (1975) exposed phytohemagglutinin-stimulated human lymphoctes to various concentrations of sodium arsenate, ranging from 0.05 to 100 ug/ml of culture medium, for 24 hours. Radioactively labeled triphosphates and amino acids were also added to the cultures. The incorporation of ^{14}C-thymidine into DNA was inhibited at a lower dose than the incorporation of ^{14}C-uridine into RNA. This confirmed the previous study by Petres et al. (1974). The incorporation of ^{14}C-TTP into DNA was inhibited to the same extent as ^{14}C-thymidine. ^{14}C-UTP incorporation into RNA was similar to that of ^{14}C-uridine only at levels below 1.0 ug of sodium arsenate per ml of culture medium. At higher doses, the incorporation of ^{14}C-UTP was inhibited less than that of ^{14}C-uridine.

The inhibition of incorporation of ^{14}C-ATP with increasing sodium arsenate doses was parallel to the incorporation of ^{14}C-UTP and ^{14}C-TTP up to a concentration of 10 ug/ml. Above this concentration, the incorporation of labeled ^{14}ATP into nucleic acids was greater than ^{14}C-TTP and less than ^{14}C-UTP.

A decrease in the incorporation of ^{14}C-alanine and ^{14}C-leucine into cellular protein was not found below a sodium arsenate concentration of 10 ug/ml. Even at the higher doses, there was less inhibition of incorporation than that of the labeled triphosphates and nucleosides.

Tsuda (1974) exposed L strain mouse fibroblast cells to three concentrations of sodium arsenate (0.5×10^{-4} M, 10^{-4} M, and 0.33×10^{-3} M) from 1 to 48 hours. The effects on each phase of mitosis were determined by changes in the mitotic index (# mitoses per 100 cells). As the concentration of sodium arsenate increased, the indices for prophase, metaphase, and mitosis increased compared to the control values. The telophase index decreased, while the index for anaphase remained in the control range of values. Complete recovery of cells exposed to sodium arsenate for one hour appeared to be delayed for approximately six hours. There was also no apparent increase in the mitotic index over the control index.

(3) Reproductive and Fetotoxic Effects in Mammalian and Avian Species

40 CFR 162.11(a)(3)(ii)(B) provides that a rebuttable presumption shall arise if a pesticide "(p)roduces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety." This section reflects concern that chronic exposure to chemicals may result, among other things, in injury to the reproductive system and/or the fetus and provides that a rebuttable presumption shall arise if chronic chemical exposure in test animals produces such results.

Studies discussed in this report (and summarized in Table 24) show that both trivalent (arsenite) and pentavalent (arsenate) forms of inorganic arsenic can act as teratogenic agents. The Agency concludes that, without exception, a rebuttable presumption against registration exists for all inorganic arsenical pesticides based on the teratogenic effects criteria. This decision takes into account anticipated exposure to inorganic arsenical pesticides as discussed in Section III.

Beaudoin (1974) gave single intraperitoneal injections of sodium arsenate in distilled water to pregnant Wistar rats on one of days 7 through 12 of gestation. The dosage level of sodium arsenate ranged from 20 to 50 mg/kg of body weight. The embryolethal and teratogenic effects of sodium arsenate were dose-dependent and peaked on days 9 and 10 of treatment. Resorption of fetuses was day- and dose-dependent. The percentage of resorbed fetuses was the highest at 40 mg/kg and peaked for treatment on day 9. Fetal weights for days 8, 9, and 11 of treatment were significantly less ($p < 0.01$) than the controls.

The frequency of malformed fetuses markedly increased when the dosage went from 20 to 30 mg/kg. Little additional fetal malformations occurred with 40 mg/kg. The greatest degree of fetal abnormality occurred on day 9 of gestation. A dose of 50 mg/kg of sodium arsenate was lethal to embryos for all days (7 through 12) of treatment. Teratogenic effects were not observed in fetuses treated with 20 or 30

Table 24. Summary of Studies on Inorganic Arsenic Teratogenicity in Animals.

Authors	Chemical(s)	Test Animal	Treatment: Gestation Day(s) Treated / Day(s) Sacrificed	Dosage (mg/kg)	Effects
Beaudoin 1974	Sodium arsenate	Wistar rat	ip 7 - 12 / 20	20 - 50 single dose	Fetal resorption and malformation were dose-dependent and peaked on treatment days 9 and 10. 50 mg/kg was lethal to all embryos. There were no teratogenic effects on days 7 and 11 and few on day 12. Malformations: eye defects, exencephaly, renal agenesis, rib and vertebral defects.
Burk and Beaudoin 1977	Sodium arsenate	Wistar rat	ip 9 - 11 / 20	30 - 50 single dose	Fetal resorption and malformation were greatest on day 9. Renal agenesis occurred mainly from treatment on day 10. Skeletal defects occurred mainly from treatment on days 9 and 10. Fetal weights declined significantly with treatment. Malformations: exencephaly, eye defects, facial clefts, agnathia, hydrocephalus, encephalomeningocele, diaphragmatic hernia.
			ip 10 / 11 - 16	45 single dose	Renal agenesis resulted mainly from growth retardation of the mesonephric duct.
Ferm and Carpenter 1968	Sodium arsenate	golden hamster	iv 8 / 12 - 14	5,20,40 single dose	No malformations at 5 mg/kg. All fetuses killed *in utero* at 40 mg/kg. At 20 mg/kg, there were exencephalic lesions, bulging eyes, and protruding tongue and mandibles.
Holmberg and Ferm 1969	Sodium arsenate	golden hamster	iv 8 / 13	20 single dose	There was fetal resorption and malformation: exencephaly, encephalocele, cleft palate and lip, anophthalmia, ear malformations.
Ferm et al. 1971	Sodium arsenate	golden hamster	iv 8 / 15	15,17.5, 20,25 single dose	Embryo resorption and malformation were dose-dependent. Malformations: exencephaly, rib defects, genitourinary defects, anencephaly, cleft lip and palate, anophthalmia, adrenal agenesis, prognathia. Genital abnormalities were greatest in females, and cleft lip, palate, and rib abnormalities were seen primarily in males.
Hood 1972	Sodium arsenite	albino Swiss-Webster mouse (CD-1 strain)	ip (*in utero*) 7 - 12 / 18	10,12 single dose	There was a high degree of resorption and reduced fetal weights that were day and dose-dependent. Malformations were highest on days 8 to 10: exencephaly, micrognathia, open eye, defective tail, skeletal defects.

Hood and Bishop 1972	Sodium arsenate	albino Swiss-Webster mouse (CD-1 strain)	ip	$\frac{6 - 12}{18}$	25,45 single dose	At 25 mg/kg, there was no significant difference from the controls. At 45 mg/kg, there was increased resorption, especially from days 11 and 12. Fetal weights were reduced especially from days 7 and 9. Fetal malformations were highest on days 7 to 11: exencephaly, shortened jaw, protruding tongue, anophthalmia exophthalmos, open eye, umbilical hernia, tail defects, hydrocephalus, and skeletal defects.
Hood and Pike 1977	Sodium arsenate	albino Swiss-Webster mouse (CD-1 strain)	ip	$\frac{9}{18}$	40 single dose	There was a significant increase in fetal mortality, resorptions, and malformations. There was a decrease in fetal weights due to treatment.
Hood et al. 1977	Sodium arsenate	albino Swiss-Webster mouse (CD-1 strain)	ip	$\frac{9 - 10}{18}$	40	There was less effect on fetal mortality, weight, and malformation in orally treated mice than in those injected.
			oral (p.o.)		120 single dose	
Hood et al. (undated)	Sodium arsenate	albino Swiss-Webster mouse (CD-1 strain)	ip	$\frac{7 - 15}{18}$	40 single dose	There was a significant decrease of fetal weights from treatment on days 7 or 10. There was a significant increase in fetal resportion and death. (Prenatal mortality was higher than in the orally treated mice.) Treatment on days 9 or 10 resulted in increased malformations such as exencephaly, shortened jaw, open eyes, kinked tail, and skeletal defects.
			oral (p.o.)	$\frac{7 - 15}{18}$	120 single dose	There was a significant reduction of fetal weights from treatment on days 10, 11, or 15. The number of dead or resorbed fetuses increased significantly from day 11 treatment. Oral treatment did not increase significantly the incidence of gross malformation, but a trend was evident. Malformations: oligodactyly, micromelia, kinked tail. Skeletal defects increased significantly only from treatment on day 9 (same as with ip treatment).
Matsumoto et al. 1974	Sodium arsenite	mouse (ICR strain)	oral (p.o.)	$\frac{9 - 11}{18}$	10, 20 40 daily dose	There were 5.7% (10 mg/kg), 0% (20 mg/kg), and 4.2% (40 mg/kg) fetal malformations compared to 0% for controls (no statistical values given). Malformations were bent tail, cleft palate, open eyelid, and bone deformities (40 mg/kg). There was reduced fetal growth and ossification of cervical vertebrae and leg/tail bones.
			ip	$\frac{6 - 11}{18}$	5,10, 20 daily dose	There were 3.5% (5 mg/kg) and 1.3% (10 mg/kg) fetal malformations compared to 1.2% for controls (no statistical values given). Malformations were open eyelid, bent tail, club foot, and kidney deformity (10 mg/kg). As in oral treatment there was reduced growth and ossification.

Franke et al. 1936	Sodium arsenite	chicken embryo	injection	not specified	0.01 - 1.0 ppm single dose(1)	There were only ectopic abnormalities (unspecified) and these occurred at the lowest dosage. There were no abnormalities at 1.0 ppm.
Ridgway and Karnofsky 1952	Potassium arsenite, Arsenic pentoxide, Sodium arsenate	Leghorn chicken embryos	injection	4, 8 18	0.2 mg/egg single dose(2)	Embryos injected on the fourth day with sodium arsenate were stunted with mild micromelia and abdominal edema. There were no effects with potassium arsenite and arsenic pentoxide. There were no effects in the eight-day old embryos.
Puzanova and Doskocil 1976	Pentavalent arsenic	Leghorn chicken embryos	injection	2 - 4 varied	3ug/egg single dose(3)	Embryos treated day 2 of incubation were normally differentiated. Of embryos (19) surviving day 3 treatment, 21% had abnormalities (deformed beak, lumbar lordosis, body distortion, wrinkled brain vesicles, incomplete body walls). Thirteen (13) embryos survived day 4 treatment; 32.5% had abnormalities such as impaired mesonephros, kyphosis of body, hyperlordosis and small amnion. Compression of embryos in deformed amnion may have caused defects.
Schroeder and Mitchener 1971	Soluble arsenite salt	Charles River mouse	oral (drinking water)	through 3 generations	5 ppm ad libitum(4)	Arsenic increased the ratio of males to females and reduced the litter size.
Kimmel and Fowler (letter 1977b)	Sodium arsenate Sodium arsenite	rat	oral (drinking water)	1 - 21 21	30,90 ppm ad libitum(5)	No adverse effects.
James et al. 1966	Potassium arsenate	Yearling ewe	oral (capsule)	treated for 18, 45, 140 and 147 days	0.5 - 0.75	All lambs were normal. One lamb born to a ewe given 0.75 mg/kg (later reduced to 0.5 mg/kg due to toxicity) was very small.

Morris et al. 1938	Arsenic trioxide	Osborne - Mendel rat	oral (food)	treated from 4 wk. old to 1 yr.	27, 215 mg in diet(6)	There were no significant differences in fertility and fecundity between the experimental and control groups. This was also true of the F_1 generation when treated similarly.
Kojima 1974	Arsenic trioxide	Wistar rat	oral (food)	treated prior to and during gestation	10, 50, 100 ppm in diet(7)	No significant difference in the number of litters between treated and control rats.

1. Total As: 0.01 - 1.0 mg/kg (Franke et al. 1936).
2. Total As: 4 mg/kg (Romanoff and Romanoff 1949).
3. Total As: 0.06 mg/kg (Romanoff and Romanoff 1949).
4. Daily dose for adult females 0.56 - 2.0 mg/kg (Letter 1978).
5. Total As: 2.25-3.75 mg/kg; 6.75-11.25 mg/kg (Letter 1977b).
6. 9.2 mg/kg/day; 79 mg/kg/day (Morris et al. 1938).
7. Total As: 15.4 mg/kg; 77.1 mg/kg; 154.3 mg/kg (Kojima 1974).

mg/kg on days 7 and 11. On day 12 there were some skeletal defects. Fetal malformations included eye defects, exencephaly, renal agenesis, and rib and vertebral defects. Atlas ossification centers were absent or rudimentary in 63% of the fetuses from dams treated on day 9 of gestation.

Burk and Beaudoin (1977) found that there was a high incidence of malformations (including renal agenesis) and resorptions, both of which were dose-dependent and related to the time of treatment, in embryos from Wistar rats which had been injected intraperitoneally with sodium arsenate.

In a preliminary study, pregnant rats were given a single intraperitoneal injection of aqueous sodium arsenate (30 to 50 mg/kg of body weight) on one of days 9 through 11 of gestation. The rats were sacrificed on day 20. The number of fetal resorptions and malformed survivors (soft tissue and skeletal defects) increased with increasing concentrations of sodium arsenate for each day. The percentages of both were greatest on day 9 and decreased thereafter. Malformations that occurred primarily on day 9 of gestation were exencephaly, eye defects, and facial clefts. There were also cases of agnathia, hydrocephalus, gastroschisis, encephalomeningocele, and diaphragmatic hernia. Day-10 treatment resulted primarily in urogenital system defects. Skeletal malformations occurred primarily on days 9 and 10. Fetal weights declined as the concentration of sodium arsenate increased.

In the second experiment to study renal agenesis, the pregnant rats were injected with 45 mg/kg on day 10 of gestation. This was the most effective dose for production of renal agenesis, with minimal embryonic death. The rats were sacrificed on days 11 through 16. The first abnormal fetuses (from day-12 treatment) showed growth retardation of the mesonephric duct. For treatment days 13 through 16, retardation of the duct eventually prevented formation of the ureteric bud and resulted in renal agenesis. In some cases the mesonephric duct failed to connect with the cloaca, and there was degeneration of the metanephric blastema. Gonadal agenesis was not observed in any of the embryos from treated rats, but in some cases there was incomplete descent of the testes.

Ferm and Carpenter (1968) intravenously injected either 5, 20, or 40 mg/kg of sodium arsenate in distilled water into the lingual vein of pregnant golden hamsters (*Cricetus auratus*) on the eighth day of gestation. Control animals received only distilled water. The hamsters were sacrificed on days 12 through 14. All embryos died *in utero* at 40 mg/kg of sodium arsenate. Exencephalic lesions were induced at 20 mg/kg of body weight, and no malformations occurred with 5 mg/kg. The exencephalic lesions were markedly consistent and specific, and often within a litter a majority of the survivors showed strikingly similar defects. Other effects included bulging eyeballs and protruding tongue and mandibles. Histological examination of the placental membranes showed no abnormalities.

Holmberg and Ferm (1969) injected a sublethal dose (20 mg/kg) of sodium arsenate into the lingual vein of pregnant golden hamsters (*Cricetus auratus*) on the eighth day of gestation. After sacrifice on the thirteenth day, the embryos exhibited several types of malformations, and the most prominent of these in all litters was exencephaly. Other abnormalities included encephalocele, cleft palate and lip, unilateral and bilateral microanophthalmia, and ear malformations. Sodium arsenate induced a total of 49% malformed embryos and 35% resorbed embryos.

Ferm et al. (1971) injected sodium arsenate intravenously into pregnant golden hamsters (*Cricetus auratus*) at three different times on the eighth day of gestation. The three groups were treated with sodium arsenate at 9 AM, 3 PM, and 9 PM (6-hour intervals) at the following doses (mg/kg): 15, 17.5, 20, and 25 (9 PM only). Control hamsters were injected intravenously with similar volumes of demineralized water. The females were sacrificed on the morning of the 15th day of gestation.

Within each of the three periods of treatment, the rate of embryo resorption and malformation increased with increasing doses of sodium arsenate. A comparison of the three groups showed that the resorption rate decreased the later the time of treatment on the eighth day of gestation.

The rate of malformation did not follow a similar pattern except at 15 mg/kg sodium arsenate. Malformations were slightly more frequent in the 9 PM group at the higher doses. A marked increased in rib malformations accounted for this high malformation rate in the 9 PM period. The overall malformation rate remained constant for all three periods of treatment. Fetal malformations that occurred most frequently included exencephaly, rib malformations, genito-urinary abnormalities, and anencephaly. Other effects seen less frequently were cleft lip and palate, anophthalmia, adrenal agenesis, and prognathic embryos. Cleft lip and palate and rib abnormalities were significantly more frequent in males, and genital abnormalities occurred more frequently in female embryos. The sex ratio for the total malformation rate was close to 1.0.

Hood (1972) gave pregnant albino Swiss-Webster mice single intraperitoneal injections of either 10 or 12 mg of sodium arsenite in distilled water per kg of body weight on one of days 7 through 12 of gestation. Controls were injected with an equivalent volume of distilled water. All mice were sacrificed on the 18th day of gestation. Treatment of the pregnant mice with sodium arsenite resulted in a significant ($p < 0.05$) increase in fetal deaths for all days 7 through 12 at both dosage levels studied. Most deaths apparently occurred shortly after treatment as determined by the degree of resorption. There was a significant ($p < 0.05$) decrease in fetal weights that was day- and dose-dependent. The higher doses tended to induce a greater effect. The period of greatest susceptibility to teratogenic effects was gestation days 8 through 10. On these days there was a significant ($p < 0.05$) difference from the control value. The most common malformations were exencephaly, micrognathia, open eye, and bent, short, or missing tails. The major skeletal defects were fusion of the ribs and fused or missing vertebral ossification centers. These malformations were found only in fetuses from the groups treated on days 8 through 10 (rib defects) and on days 9 to 10 (vertebral anomalies).

Hood and Bishop (1972) gave single intraperitoneal injections of 25 or 45 mg of sodium arsenate per kg of body weight to pregnant albino Swiss-Webster mice on one of days 6 to 12 of gestation. Controls received an equivalent dose of distilled water. The mice were sacrificed on the eighteenth day of gestation.

In females injected with 25 mg/kg of sodium arsenate, the rates of fetal resorption and malformation were not significantly different from those found in the controls.

Intraperitoneal injections of 45 mg/kg, particularly on treatment days 11 and 12, consistently resulted in significantly increased fetal resorption. Treatment on days 6 through 11 resulted in decreased fetal weights compared to controls ($p < 0.05$). Reduction in fetal weights was the most severe on treatment days 7 and 9. Sodium arsenate induced several fetal malformations that were somewhat day-dependent. Among these were exencephaly, shortened jaw, protruding tongue, anophthalmia, exophthalmos, open eye, umbilical hernia, shortened tail, twisted tail, hydrocephalus, fusion of ribs, forking of ribs, and fusion of vertebrae. The percentage of grossly malformed fetuses, resulting from treatment on the sixth day of gestation, was very low compared to that for days 7 to 11. Treatment on day 12 resulted in the resorption of most fetuses, but those that survived were morphologically normal.

Hood and Pike (1972) found that intraperitoneal injections of sodium arsenate in Swiss-Webster mice on the ninth day of gestation resulted in a significant increase in fetal mortality and malformation and decrease in fetal weight.

Treatment of pregnant mice consisted of single intraperitoneal injections of 40 mg of sodium arsenate in distilled water per kg of body weight. Control mice were injected with water or were not treated at all. All females were sacrificed on the eighteenth day of gestation. The fetuses from treated females had a high rate of resorption and death, gross malformations and skeletal defects, and had greatly reduced fetal weights compared to the fetuses of the controls.

Preliminary work in mice by Hood et al. (1977) showed that the intraperitoneal administration of sodium arsenate had a greater adverse effect on prenatal mortality, fetal weights, and morphological development than oral administration. On gestation days 9 and 10, pregnant albino Swiss-Webster mice (CD-1 strain) were treated with sodium arsenate in distilled water either intraperitoneally (40 mg/kg of body weight) or orally (120 mg/kg). Controls were treated with distilled water. The animals were sacrificed on gestation day 18. The maternal death rate was similar for both treatments, indicating similar levels of toxicity to the females. A dose of 120 mg/kg of sodium arsenate orally administered was required to obtain adverse prenatal developmental effects. There was a much lower level of fetal malformation in the orally treated mice than in those injected intraperitoneally. The intraperitoneal treatment resulted in decreased fetal weights, compared to the controls.

This effect was seen in the oral treatment only when given on day 10 of gestation.

Hood et al. (Undated) administered sodium arsenate orally to pregnant albino mice (CD-1 strain) on one of gestation days 7 through 15. Sodium arsenate was also administered intraperitoneally to other pregnant mice as a positive control. Preliminary studies with oral doses of 40, 50, 60, 80, and 100 mg/kg of sodium arsenate showed no significant differences in effects from the negative controls (water only). Sodium arsenate was then either orally (120 mg/kg) or intraperitoneally (40 mg/kg) administered to pregnant mice on the same series of days.

Compared to the negative controls, dead and resorbed fetuses from orally treated mice increased significantly only on day 11 ($p \leq 0.01$). In the positive control group, however, treatment on days 7, 8, 9, and 11 ($p \leq 0.05$) and 10, 13, 14, and 15 ($p \leq 0.01$) resulted in a significant increase in the number of dead and resorbed fetuses compared to the negative controls. The positive controls (ip) also had a higher prenatal mortality than the groups treated orally on days 7, 11, or 13 ($p \leq 0.01$) and 14 ($p \leq 0.05$).

The incidence of gross malformations from oral treatment did not increase significantly over the negative control values, although the results were suggestive of such an effect. However, intraperitoneal treatment on days 9 ($p \leq 0.01$) and 10 ($p \leq 0.05$) resulted in an increase in malformations over the negative control values. The gross malformations that occurred most frequently with oral treatment were oligodactyly, micromelia, and kinked tail. Those associated with ip treatment were shortened jaw, exencephaly, open eyes, and kinked tail.

Skeletal malformations resulted from either oral or intraperitoneal treatment on day 9 and were significantly increased ($p \leq 0.05$) over the negative control values. Fewer defective fetuses were seen in litters from treatment on other days. The most common defect was fused ribs with some cases of fused vertebrae. There was no significant incidence of visceral defects.

Compared to the negative controls (water only), oral treatment resulted in significantly lower fetal weights on treatment days 10 and 11 ($p \leq 0.01$) and 15 ($p \leq 0.05$). Fetuses from females that received sodium arsenate by injection on days 7 or 10 ($p \leq 0.05$) or 9 ($p \leq 0.01$) weighed significantly less than those from females receiving only water.

Matsumoto et al. (1974) studied the effect of sodium arsenite on fetuses of pregnant ICR mice that were given the compound orally or intraperitoneally. One group of mice was given 10 or 20 mg of sodium arsenite/kg (body weight) intraperitoneally (ip) once a day on days 6, 7, and 8 after conception. Another group received 5 or 10 mg/kg (ip) once a day on days 9, 10, and 11 after conception. A third group was given 10, 20, or 40 mg/kg orally once a day on days 9, 10, and 11 after conception.

The percentage of malformed fetuses from ip-treated pregnant females was 3.5% (5 mg/kg) and 1.3% (10 mg/kg) compared to 1.2% for the controls (no statistical values given). The percentage of resorbed or dead fetuses was 7.3% (controls), 12.1% (5 mg/kg), and 45.3% (10 mg/kg). In the group of orally treated mice, the percentage of malformed fetuses was 5.7% (10 mg/kg), 0% (20 mg/kg), and 4.2% (40 mg/kg) compared to 0% for the controls (no statistical values given). The percent of resorbed or dead fetuses was 9.8% (controls), 4.5% (10 mg/kg), 5.5% (20 mg/kg), and 30.4% (40 mg/kg).

The malformations observed with oral treatment were bent tail, cleft palate, open eyelid, and bone deformities (40 mg/kg only). Malformations from ip treatment were open eyelid, bent tail, club foot, and kidney deformity (10 mg/kg only). From both ip and oral treatment there was reduced fetal growth and reduced ossification of cervical vertebrae and leg and tail bones.

Franke et al. (1936) tested the effect of sodium arsenite on the development of chick embryos. Sodium arsenite was injected into the eggs at the following concentrations: 0.01, 0.05, and 0.10 ppm. There were no dead chicks in the group that received 0.01 ppm, but 6.7% had abnormalities of ectopic form (unspecified by the authors). At 0.05 ppm, 14.3% of the embryos were dead, and 14.3% of the survivors were abnormal. In the group that received 0.1 ppm of sodium arsenite, 83.3% of the embryos were dead. However, there were no abnormalities in the surviving chicks.

Ridgway and Karnofsky (1952) injected four- and eight-day-old white Leghorn chicken eggs with potassium arsenite, arsenic pentoxide, and sodium arsenate. When examined on the eighteenth day of incubation, 50% of the chicken embryos, injected via the yolk sac on the fourth day with 0.2 mg/egg of sodium arsenate, were stunted and showed mild micromelia and abdominal edema. This did not occur in the embryos injected on the eighth day. Potassium arsenite and arsenic pentoxide did not produce these effects.

Puzanova and Doskocil (1969) studied the effects of a pentavalent arsenical on white Leghorn chicken embryos. The embryos were given a single dose of 3 ug of arsenic subgerminally or intraaminally on either day 2, 3, or 4 of incubation. The embryos were collected at various times, then fixed and stained.

All embryos from day 2 treatment (collected on 8th day) survived the arsenic application and were normally differentiated.

Of those treated on day 3, 5 died and 19 survived. The dead embryos (collected 12 to 24 hours after treatment) showed abnormalities in the circulatory system (dilatation of vessels, extended heart, hemorrhaging in head and body) and in the brain vesicles (wrinkling). Of the surviving embryos (collected between incubation days 4 and 9), one had a deformed beak, and three had lordosis of the spinal lumbar region. Lordosis indicates a disturbance of amnion development resulting in compression of the embryo in the amnial pouch. There was also some wrinkling of the brain vesicles, body distortion, and inadequate formation of body walls. The other 15 embryos were differeniated normally but were smaller than the control embryos.

From day 4 exposure, 19 embryos died and 13 survived. The dead embryos were collected 12 to 72 hours after treatment. Twelve (12) had circulatory disorders (venostasis, heart dilatation, hemorrhaging), and others showed hyperlordosis, body distortion, wrinkled brain vesicles, and small amnion. Of the 13 survivors, 9 were normal, and 4 showed abnormalities such as impaired mesonephros, kyphosis of the body, hyperlordosis with scoliosis, and small, tight amnion.

In a study by Schroeder and Mitchener (1971), Charles River CD strain mice were bred in special facilities to avoid contamination from trace elements. At the time of weaning, five pairs of mice were selected randomly, fed special food, and given doubly deionized forest spring water. Drinking water containing 5 ppm of a soluble salt of arsenite (form not specified by author) was continuously available to the mice. The control mice received plain deionized water. The mice were allowed to breed at will for six months. Arsenite at this dose level did not affect the rate of growth or long-term survival and did not cause early mortality. In three successive generations of mice, arsenite given via drinking water resulted primarily in an increased ratio of males to females and in a reduction of the litter size.

The following studies showed no teratogenic effects in laboratory animals exposed to various inorganic arsenicals.

Kimmel and Fowler (Letter 1977b) gave pregnant rats either sodium arsenate or sodium arsenite in their drinking water (ad libitum) from gestation day 1 through 21 at exposure levels of either 30 or 90 ppm. There were no adverse effects on fetal weights, number of fetuses per litter, or number of malformations.

James et al. (1966) fed four pregnant yearling ewes potassium arsenate via gelatin capsule. The first ewe received 0.75 mg/kg daily from the first day of gestation.

However, after 18 days, the animal developed toxicosis, and the treatment was discontinued. A second ewe received 0.50 mg/kg daily for the first 45 days of gestation. The remaining two ewes were given 0.50 mg/kg of the salt for the entire gestation period (140 and 147 days respectively). The first ewe gave birth to "a full-term but hairy lamb" that weighed only 1.6 kg. The three other ewes produced normal lambs. Analysis of bone and soft tissue samples indicated that arsenate did not accumulate in detectable amounts in ewes fed arsenic throughout gestation or in lambs from ewes on the reduced treatments.

Morris et al. (1938) fed Osborne-Mendel rats and their offspring a diet containing either 26.8 or 215 mg of arsenic trioxide (approximately 9.2 and 79 mg/kg per day. respectively). The animals were fed the special diets ad libitum from four weeks of age to approximately one year of age.

The rats (P_1) were divided into two groups, one for each dose level. Each group contained 36 rats: 18 controls (9 of each sex) and 18 experimental rats (9 of each sex). The control animals received a diet that was adequate for growth and reproduction. The experimental groups were fed the same diet with the addition of arsenic trioxide. Both groups of rats were mated at ages of 90 to 110 days as follows: control female x control male, control female x experimental male, experimental female x control male, experimental female x experimental male. Pairs of rats were placed in cages and given the control diet during the mating period, with the exception of experimental females with experimental males. Males were removed from the cages after females showed a positive smear for sperm.

The second generation (F_1) of rats was taken from the second litter of the P_1 females. These animals were given the same diet as their respective parent of the same sex. The mating patterns used for the P_1 groups were also used for the F_1 groups. Only one litter was obtained from this generation. The same patterns of mating were used again for the F_2 group.

No differences in fertility or fecundity were observed between the various experimental groups of both generations (P_1 and F_1) and the control groups. The average weights of P_1 females and their offspring showed no significant differences from the controls.

Kojima (1974) raised groups of male and female albino Wistar rats (P_1) and their offspring (F_1) on a diet containing arsenic (unspecified form, but measured as As_2O_3).

Different groups received various doses of arsenic (10, 50, and 100 ppm), and for each dose level there were five test groups of rats. Group I rats and their offspring received the control diet. Group II received the control diet; and after delactation, the young received the arsenic diet. Group III rats were fed the experimental diet, but the young were given the control food. Group IV rats received the experimental diet, but after delactation the offspring were given the control food. Group V rats and their offspring were fed only the arsenic diet.

The actual amount of arsenic ingested was determined by total food consumption. The P_1 rats each consumed an average of 270 g of food. The arsenic levels consumed by P_1 rats in Groups III, IV, and V were 2.7, 13.5, and 27 mg (10, 50, and 100 ppm respectively). Prior to delactation, F_1 rats of Groups IV and V ingested 0.5, 2.5, and 5 mg (10, 50, and 100 ppm respectively). After delactation, F_1 rats of Groups II and V ingested 10, 50, and 100 mg (10, 50, and 100 ppm respectively).

There were no differences in the number of litters between P_1 rats fed experimental diets containing arsenic and the control group of rats. The young of females raised on the diet containing 100 ppm of arsenic showed no effects in histopathological tests, breaking strength of bones, and Ca and P content of bones and teeth.

Pregnant mice, orally treated with 120 mg/kg of sodium arsenate (Hood et al. 1977; Undated) or 10 mg/kg sodium arsenite (Matsumoto et al. 1974), gave birth to young exhibiting both gross malformations and skeletal defects. Mice given sodium arsenite at 5 ppm in drinking water showed a reduction in litter size over three generations.

Based on these studies and the discussions in Section IV.A, the Agency concludes that there is sufficient evidence for the teratogenic effects of both trivalent inorganic arsenic (arsenite) and pentavalent inorganic arsenic (arsenate). Also there is evidence for the reproductive effects of trivalent inorganic arsenic.

In order to determine whether a rebuttable presumption should be issued on each inogranic arsenical based on these effects pursuant to Section 162.11(a)(3)(ii)(B), the Agency must determine whether an ample margin of safety exists between the levels of arsenate and arsenite which produce these effects and the levels to which humans can reasonably be anticipated to be exposed.

The levels of arsenate and arsenite which produce teratogenic effects discussed in this section of the position document are tabulated in Table 24. Of particular interest are the studies by Hood et al. (1977; Undated) and Matsumoto et al. (1974) in which arsenite or arsenate were administered orally to mice.

In the study by Matsumoto et al. (1974), arsenite was administered orally at dosages as low as 10 mg/kg. At this dosage several malformations (teratogenic effects) were observed including bent tail, cleft palate, and open eyelid. In addition to these effects the author observed reduced fetal growth, and reduced ossification of cervical vertebrae and leg and tail bones. The author did not determine a dosage level (NEL) at which teratogenic effects were not observed.

In the study by Hood et al. (1977; Undated), arsenate was administered orally to mice at 120 mg/kg. This dosage produced skeletal malformations such as fused ribs and some cases of fuses vertebrae. A dosage of 100 mg/kg (NEL) did not produce significant differences from controls.

In order to determine whether an ample margin of safety exists for each inorganic arsenical, the Agency must determine how much of each a 60-kg woman would be exposed to through oral, dermal, and/or inhalation exposure. These determinations were made in the Exposure Analysis (see Section III), and the results are duplicated here (Table 25).

For purposes of this analysis the margin of safety will be defined as the level (dosage in mg/kg) which produced no observable effect (NOEL) divided by the anticipated exposure:

$$\text{Margin of Safety} = \frac{\text{NOEL}}{\text{Exposure}}$$

In case of inorganic arsenate the NOEL is 100 mg/kg (Hood Undated). For inorganic arsenite, however, all dosages tested produced teratogenic effects (Matsumoto et al. 1974). Therefore, because the NOEL has not been established for inorganic arsenite the lowest effect level [10 mg/kg (Matsumoto et al. 1974)] will be used in the calculation of the margin of safety for inorganic arsenite. It should be noted that if the NOEL for arsenite is found to be only slightly less than 10 mg/kg, this could represent a significant decrease in the corresponding margin of safety. The margin of safety for each use situation discussed in the exposure analysis has been calculated and can be found in table 25.

Table 25. Summary of the Total Theoretical Exposure To Inorganic Arsenic Resulting From the Use of Inorganic Arsenical Pesticides

Chemical or Use Situation	Total Theoretical Exposure (for a 60-kg Woman in mg/kg)	Margin of Safety
Agricultural Situations		
Sodium Arsenite (trivalent)	5.5	1.8
Arsenic Acid (pentavalent)	2.72	37
Sodium Arsenate (pentavalent)	0.65	154
Copper Acetoarsenite (trivalent)	0.32	31
Calcium Arsenate (pentavalent)	0.17	588
Arsenic Trioxide (trivalent)	0.68	15
Lead Arsenate (pentavalent)	0.66	152
Wood Preservative Situations (Sodium Pyroarsenate (Arsenic Trioxide*, Arsenic Pentoxide, Sodium Arsenate, Arsenic Acid, and Ammonium Arsenite*)		
Large Industrial Situations		
Inhalation Exposure	0.05	2000
Dermal Exposure	0.57 - 9.0	11 - 175
Intermittent Application to Wood During On-Site Construction		
Dermal Exposure to Ammonium Arsenite	1.1	91
Exposure From Handling, Sawing, Fabricating, etc, of Treated Wood Products		
Inhalation Exposure	0.27	370
Dermal Exposure	0.24	417
Exposure To Individuals Living or Working In Dwellings Containing Arsenic-Treated Wood		
Inhalation Exposure	7×10^{-7} - 0.002	5×10^{4} - 1.4×10^{8}
Dermal Exposure	0.03 - 2.59	39 - 3333

* During the formulation of wood preservatives, all trivalent arsenic is oxidized to pentavalent arsenic; therefore, the NOEL for arsenate (100 mg/kg) was used in calculating the margin of safety for all wood preservatives.

It is generally recognized that humans vary in their susceptibility to a toxicant and that humans may, for a variety of reasons, be more sensitive than laboratory animals. Therefore, the Agency concludes that an ample margin of safety does not exist for any use of the inorganic arsenicals and recommends that a rebuttable presumption be issued against the following: ammonium arsenite, arsenic acid, arsenic pentoxide, arsenic trioxide, calcium arsenate, copper acetoarsenite, lead arsenate (basic and standard), sodium arsenate, sodium arsenite, and sodium pyroarsenate.

V. OTHER RELEVANT ADVERSE EFFECTS

This section addresses certain criteria for determination of unreasonable adverse effects which arsenic may produce, but for which insufficient evidence exists to initiate a rebuttable presumption. The Agency requests registrants or other interested persons, having information on these or any other possible adverse effects of inorganic arsenic, to submit such data to the Agency.

A. Delayed Neurotoxicity

Landau et al. (1977) did a pilot study of male workers in a copper smelter using ores high in arsenic (previously studied by Milham and Strong, and Pinto and McGill). Three groups of men were studied. The first group were workers from an area of high arsenic exposure who had 200 ug/liter of arsenic in urine samples for at least the last five years. The second group were workers from a low arsenic exposure area, and the third group consisted of workers from an aluminum plant (no arsenic exposure) and from non-industrial settings.

The men received a clinical and a neurological examination and completed a personal questionnaire. Samples of their blood, urine, hair, and nails were taken. The neurological examination consisted of sensory and/or motor nerve conduction studies on three nerves: the right ulnar (sensory and motor), the right common peroneal (motor), and the right sural (sensory). Both conduction and amplitude were measured for each nerve using standard techniques with surface electrodes.

Urinary arsenic levels corresponded well with worker exposure to arsenic. Nail and hair analyses also clearly distinguished the test groups. Blood arsenic was determined not to be a useful measurement of arsenic exposure.

Exposure to other metals was also investigated. Copper in the blood and urine did not differentiate the groups, while copper levels in the hair did. Cadmium, nickel, and zinc levels in nail tissue were highest in both of the smelter worker groups. Lead values in urine, blood, nails, and hair were generally highest in the smelter workers.

Neurological findings were based on a clinical examination for neuropathies and an objective electrical measurement. From a preliminary analysis, a dose-response relationship was not clearly evident. There was a weak association between the clinical and the objective electrical measurements of the neurological status of each man. A multivariate analysis was used to further study the association of neurological abnormalities from exposure to arsenic and other metals. There was a relationship between lower ulnar sensory amplitude, lower peroneal conduction velocity, and lower peroneal amplitude at the ankle and knee with higher levels of arsenic in urine, hair, and nails.

After further analysis, the authors concluded that there is a statistically significant relationship between arsenic levels (exposure) in body tissues and reduced neurological response. The clinical examination showed that a higher percentage of the smelter workers had some form of neuropathy compared to the control group. This was after diabetes, trauma, cigarette and alcohol use, use of drugs, and other relevant factors were taken into account. The authors also discussed the various sources of error in the study such as individual day-to-day variability, proximity of workers' homes to the smelter stack, and the effect of age on the neurological responses tested.

Mizuta et al. (1956) reported on 220 patients of all ages who had been poisoned by contaminated soy sauce, with an average estimated ingestation of roughly 3 mg of arsenic (probably calcium arsenate) daily for two to three weeks. In this group, 85% had facial edema and anorexia; fewer than 10% had exanthemata, desquamation, and hyperpigmentation; and about 20% had peripheral neuropathy. Although the majority of the patients' livers were enlarged, relatively few abnormalities were found in liver-function tests; the histopathologic description of five liver biopsies did not reveal severe degenerative changes. There were no findings suggestive of congestive failure, but tions were made of 124 patients in another district.

The exposed group had a statistically significant higher rate of the following problems compared to the two control groups. There was apparently no distinct difference between these groups in their prenatal and postnatal development before ingestion of the contaminated milk. The victims had a lower intelligence quotient than their brothers and sisters. Among mentally retarded children in one district, the victim group had a higher rate of severe retardation (IQ below 50) than children who had not consumed the arsenic-tainted milk. The victims showed growth retardation from the age of one year to school age compared to the other groups. There was a higher prevalence of myopia; abnormal EEG findings; higher DMF rate (number of decayed, missing, or filled teeth); and abnormal X-ray findings in facial shape. Although not statistically significant, there was a higher rate of the following problems: mortality, abnormal ophthalmoscopic findings, growth retardation during the school years, retardation of skeletal growth (including finger size), higher peridontal disease rate, narrow vision range, and abnormal X-ray findings in teeth. The authors concluded that the victims were still suffering from many physical and mental disorders after 17 years.

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electrocardiograms were abnormal in 16 of 20 patients. The patients' symptoms tended to diminish after five or six days, despite continued intake of arsenic, and neurologic symptoms became prominent as much as two weeks after arsenic ingestion was discontinued, at which time urinary arsenic content remained high. Hair was found to contain arsenic at 2.8 to 13.0 ppm near the root, compared with 0.4 to 2.8 ppm in hair near the root from control patients.

Ohira and Aoyama (1973) organized an epidemiological study on babies that drank arsenic-tainted milk in 1955 in Japan. The number of victims was 12,159, of whom 131 died. The disaster was caused by an arsenic-contaminated milk stabilizer.

A survey was made of 414 people of whom 74 were given medical examinations. A questionnaire collected in 1955 was rereviewed. Comparative studies were done on the victims and their brothers and sisters, and on handicapped children in institutions (born from 1953 to 1955) who drank arsenic-tainted milk, those who drank a noncontaminated powdered milk, and those who were fed only maternal milk. Another study was done on children (born between 1954 and 1955) in a district where good records had been kept of their physical growth and mental development through school. They were divided into the same groups as the above study. Examina-

B. Hazard to Wildlife

(1) Population Reductions in Nontarget Aquatic Organisms

40 CFR Section 162.11(a)(3)(ii)(C) provides that a "rebuttable presumption shall arise if a pesticide's [use]...[c]an reasonably be anticipated to result in significant local, regional, or national population reductions in nontarget organisms...."

Menhinick (1962) listed the following possible adverse effects which may result from introduction of pesticides into various ecosystems: a decrease in the number of species and/or genera, a decrease in number and species of large organisms, a compensating increase in numbers of tolerant species, and a shift in trophic structure in favor of lower trophic levels.

When sodium arsenite was registered for use as an aquatic herbicide, it was recommended that arsenic content in treated fresh water not exceed 0.05 ppm (Goudey 1946); a limit of 10 mg/liter [ppm] of arsenic contamination has been recommended for estuarine waters (Lincer 1975).

Except for use of copper acetoarsenite in mosquito control programs, there are no inorganic arsenicals registered for aquatic uses. Indirect sources of arsenic contamination of fresh and marine/estuarine waters, which may adversely affect aquatic organisms, include drift and runoff from agricultural application of inorganic arsenicals, as well as use of wood (for pilings and docks) treated with inorganic arsenical wood preservatives.

(a) Phytoplankton, Zooplankton, and Invertebrates

Reduction in populations of plankton and aquatic invertebrates can have indirect adverse effects on higher organisms by reducing numbers of oxygen-producing algae and through depletion of food sources (Ball and Hooper 1966).

Surber and Meehan (1931) conducted experiments which showed that 2.0 ppm arsenious oxide [arsenic trioxide] equivalent in a commercial sodium arsenite formulation would not kill important fish food organisms. The most sensitive species were chironomid larvae, mayfly nymphs, and fresh water shrimp; these species showed relatively high mortality rates on exposure to 2.5 to 4 ppm As_2O_3. Other studies, however, have shown that use of sodium arsenite can reduce numbers of fish food

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organisms. Lawrence (1958) performed studies which showed that two applications to experimental ponds of 4 ppm As_2O_3 as sodium arsenite one month apart reduced the number of bottom invertebrates an average of 34% as compared to control ponds; two applications of 8 ppm As_2O_3 one month apart reduced bottom invertebrates an average of 45% as compared to controls. An application of 4 ppm As_2O_3 one year later to the ponds which had received two applications of 4 ppm resulted in an average increase of 33% in bottom organisms; application of 4 ppm to ponds which had received two applications of 8 ppm, however, resulted in an average decrease of 20% in bottom organisms. The authors also noted that an application of 4 ppm As_2O_3 as sodium arsenite to experimental ponds had killed all the microcrustacae and greatly reduced the population of rotifers.

Cowell (1965) studied the effects of sodium arsenite on plankton populations in farm ponds. At concentrations of 4 ppm during two successive years, sodium arsenite significantly decreased zooplankton populations from at least one sampling depth in three of four treated ponds during the first year; during the second year, sodium arsenite at 4 ppm significantly reduced zooplankton populations, especially rotifers.

Ball and Hooper (1966) studied the effects of ^{74}As-labelled sodium arsenite on pond ecology. A pond with 1/3 acre surface area and a depth of 2 meters was treated with 8 ppm sodium arsenite. Results of the pond study showed that the treatment destroyed a major portion of the phytoplankton. In addition, the number and volume of bottom invertebrates was reduced; reduction ranged from 57% for dragonflies to 100% for mayflies. The authors concluded that sodium arsenite "persists in the ecosystem at low concentration levels and that it has an adverse effect upon many components of the system. Sodium arsenite kills many organisms important to the economy of the pond and modifies the primary producers to such an extent that production is seriously affected."

Gilderhus (1966) also studied the effects of sodium arsenite, at sublethal concentrations, on bottom invertebrates and plankton (Table 26). Nine concrete ponds, with surface measurements of 0.01 acre, were treated with varying concentrations of sodium arsenite over a 16-week period. Table 26 shows the results of the these treatments on bottom organisms and microorganisms.

Table 26. Effects of Arsenic Treatments on Populations of Invertebrates and Microorganisms

Pool	Total Sodium Arsenite Applied (ppm)	Avg. # Bottom[a] Organisms per sq ft	Avg. # Micro-[b] organisms per liter
1	4.0	24.7	3,707
2	1.2	99.0	2,328
3	0.4	68.1	3,194
4	4.8	27.9	417
5	1.6	73.4	2,643
6	0.0	58.9	1,211
7	19.2	6.3	178
8	6.4	21.3	1,754
9	0.64	64.1	1,847

[a] Ten families were represented: Oligochaeta, Nematomorpha, Ephemeroptera, Odonata, Coleoptera, Hemiptera, Chaoborinae, Tendipedidae, Ceratopogonidae, and Tabanidae.
[b] Populations counted were rotifers, Cladocera, copepods (adults and nauplii), and microcrustaceans.

Gilderhus (1966) noted that the average numbers of bottom invertebrates in pools at the four highest treatment levels were less than one-half the average found in the other treated pools and control. With regard to plankton, the two pools with the highest treatment levels had substantially reduced average numbers of microorganisms, particularly rotifers. The author also stated that total numbers of microcrustaceans, which are valuable fish foods, appeared greatly reduced in all pools which received totals of 4 ppm or more.

(b) Fish

The PERS report (EPA 1977) on inorganic arsenic (see Section I.H) lists one episode involving an unspecified arsenical in a fish kill in 1973. An unknown number of fish in a pond near a soybean field were killed. The pond had apparently been contaminated by waste cans and containers of pesticides, including linuron, alachlor, trifluralin, and paraquat. The arsenic content of the water was 73 ppm. There was insufficient evidence either to prove or disprove involvement of arsenic.

Table 27 shows the acute toxicities of sodium arsenite and arsenate to various aquatic species. Other studies indicate possible adverse effects of inorganic arsenic to aquatic organisms at levels below acute toxicity concentrations.

T[illegible] 27. Acute Toxicity of Sodium Arsenite and Arsenate to Fresh Water and Marine/Estuarine Species (in ppm)

Sodium Arsenite	24-hr	48-hr	96-hr	Reference
Daphnia sp.				
Water flea (*Daphnia pulex*)		9.1		Mackenthun 1960
Stonefly nymph (*Pteronarcys californicus*)		1.8		Cope 1966
Water flea (*Simocephalus serrulatus*)		80		Cope 1966
Channel catfish fingerlings		1.4		Cope 1966
Channel catfish-juvenile (*Ictalurus punctatus*)	47.9	25.9	25.9	Clemens & Sneed 1959
Rainbow trout		56.9	31.2	Cardwell et al. 1976
Rainbow trout (*Salmo gairdneri*)		60		Crosby & Tucker 1966
Bluegill (*Lepomis macrochirus*)		36.5		Cope 1966
Bluegill		44		Cope 1966
Bluegill-juvenile (*Lepomis macrochirus*)		44		Crosby & Tucker 1966
Brook trout (*Salvelinus fontinalis*)			72	Cardwell et al. 1976
Fathead minnows-juvenile (*Pimephales promelas*)	53.9	27.8	25.8[a]	Cardwell et al. 1976
Goldfish-juvenile (*Carassius [illegible]atus*)	36.2	31.3	27	Cardwell et al. 1976
F[illegible]ish fry (*Jordanella floridae*)	89.6	54.6	44.9	Cardwell et al. 1976
	69.8[b]		48.5[a]	Cardwell et al. 1976
Minnow (*Notropsis hudsonius*)	45	29	72[c]	Boschetti & McLoughlin 1957
Tadpole (*Adelotus brevis*)	152	119	96	Johnson 1976
Tadpole (*Limnodynastes peroni*)	108	92	60	Johnson 1976
Tadpole (*Bufo marinus*)	195	150	123	Johnson 1976
Juvenile bay scallops (*Argopecten irradians*)				
Oyster embryos (*Crassostrea virginica*)	6.50	4.40	3.49	Nelson et al. 1976
		7.50		Calabrese et al. 1973
Sodium Arsenate				
Green sunfish (*Lepomis cyanellus*)				
Daphnia sp.	175	150		Sorensen 1976a
Goldfish (*Carassius auratus*)		20		Mackenthun 1960
		32		Weir & Hine 1970

a/ 93-hr LC-50.
b 29-hr LC-50.
c/ 72-hr TL-50.

A study by Wiebe (1930) concluded that fingerling stages of four species of game fishes and three species of forage fishes exposed to concentrations of sodium arsenite ranging from 2 to 7 ppm for varying periods of time did not show any harmful effects. Species used in the study were largemouth black bass (*Micropterus salmoides*), smallmouth black bass (*M. dolomieu*), white crappie (*Pomoxis annularis*), bluegill (*Lepomis incisor*), golden shiner (*Notemigonus crysoleucas*), goldfish (*Carassius auratus*), and bullhead (*Ameiurus nebulosus*).

Since copper acetoarsenite is insoluble in water, it is generally regarded as nontoxic to fish. Bishop (1940) reported on the effects of copper acetoarsenite for mosquito control in Wheeler Reservoir in Tennessee, applied at about one pound per acre. The author noted that treatments showed no deleterious effect upon vegetation; there was no evidence of a "catastrophic destruction" of aquatic organisms important as fish food; and soil samples showed accumulation of arsenical residues in variable amounts in the bottom of reservoirs.

In another study on copper acetoarsenite, McCormick (1940) attempted to determine the amount of arsenic exposure to fish from mosquito-control dusting. Fish used in the study were mosquitofish (Gambusia patruelis), catfish (Ameiurus melas), killifish (Fundulus dispar), and silversides (Labidesthes sicculus). Fish were treated with 2 to 6 grams of pure or mixture paris green. Out of 15 series of tests, two were discarded because of procedural errors. Of the remaining 13 series of tests, eight were listed as showing positive results for arsenic residues, and five were negative. Of these, however, two series which showed positive results were rejected because the fish had not been adequately washed, and particles of copper acetoarsenite in the water could have adhered to their skin; one negative result was also rejected because tests were run only on very small, individual fish. Amounts of arsenic found ranged from trace to 0.1 mg. The author noted that Gambusia were able to withstand total dosages of 18 and 20 grams of copper aceto-arsenite (56 to 60 ppm arsenic trioxide).

Grindley (1946) studied the effects of sodium arsenite and sodium arsenate on minnows (Phoxinus phoxinus). Toxicity to fish was determined by when they had permanently overturned (i.e., lost equilibrium). At a concentration 47.5 ppm sodium arsenite, it took an average of 19 hours before fish had overturned; at 17.8 ppm, it took an average of 36 hours.

At 234 ppm sodium arsenate, it took an average of 15.85 hours before fish had overturned; at 610 ppm, it took an average of 9.05 hours. None of the fish exposed to sodium arsenite or sodium arsenate recovered after removal to fresh water. The author also noted that "smaller concentrations [of arsenic] acting over long periods in a river would [probably] damage a fishery, either by their continued action on the fish themselves or by their toxic action on other aquatic organisms which serve as the food of the fish."

Gilderhus (1966) studied some effects of sublethal concentrations of sodium arsenite on adult and immature bluegills (*Lepomis macrochirus*). Chronic toxicity to fish was based on survival, growth, hematocrit measurements, ratio of gonad weight to body weight, and pathological changes in tissues. Nine concrete pools were treated with varying concentrations of sodium arsenite over a 16-week period.

Neither hematocrit measurements nor gonad-to-body weight ratios could be related to arsenic concentration.

Survival, however, was definitely affected. In immature bluegills, survival decreased as the amount of arsenic treatment increased. Only 18% of immature fish survived after 16 weeks in a pool receiving a total treatment of 19.2 ppm sodium arsenite, compared to 90% survival in the control pool. Survival of immature fish in pools receiving totals of 1.2, 4.0, and 4.8 ppm sodium arsenite was also reduced compared to controls (54, 52, and 45%, respectively). Survival of adult bluegill was 31% in the pool receiving 19.2 ppm, compared to 60% in controls. Survival of adults in all other treated pools ranged from 50 to 62%.

Growth (length and weight gain) for immature bluegill declined as sodium arsenite concentrations increased. Adult bluegills remained about the same length during the experiment, but adults at the four highest concentrations gained less weight, on average, by four to six grams (25 to 37% of their weight at the experiment's start). Control fish, however, did not have a higher final weight than fish from some treated pools. The author could not account for this but speculated that light arsenic treatment enhanced conditions for growth.

Only adult fish from the control pool and fish from pools which received weekly treatments were examined histopathologically. Exposed fish had more hemorrhagic globes on the gills than controls. Among other symptoms noted in some exposed fish, and not seen in control fish, were fat infiltration of the liver, vacuolation of the cytoplasm of hepatic cells, foci of necrosis, and a massive extravasation of erythrocytes, which lifted the lining of the ventricle of the heart, along with interventricular fibrin and necrotic cells. In addition, in ovaries of fish from heavily treated pools, 20 to 50% of the oogonia and primary and secondary oocytes appeared as encapsulated cells. Mature ova appeared normal, but ovaries contained fewer packed cells than normal organs.

The author noted that applications of 4.0 ppm or more of sodium arsenite in one year inhibited growth of both adult and immature bluegills, and adversely affected survival of immatures. Among adults, residues of about 5.0 ppm in flesh were associated with severe loss of weight and high mortality; growth was slowed slightly with residues in flesh between 1 and 3 ppm.

Weir and Hine (1970) studied impairment of conditioned behavior of goldfish (Carassius auratus) by various metals, including sodium arsenate. Goldfish conditioned to avoid electric shocks were exposed to sublethal amounts of sodium arsenate for 24 and 48 hours. The authors found that the lowest arsenic concentration which significantly impaired conditioned behavior was 0.1 ppm, or 1/320 of the LC-50 and 1/15 of the LC-1. The authors noted that deleterious effects [i.e., impairment of conditioned behavior] were demonstrated below the arsenic levels currently accepted as safe.

Sorensen (1976b) studied thermal effects on accumulation of arsenic in green sunfish (Lepomis cyanellus). Nine groups of 20 fish each were acclimated in aquaria at 10°C [=50°F], 20°C [-68°F], and 30°C [=86°F] (three groups for each temperature level). One group at each temperature was then exposed to 0, 30, and 60 ppm sodium arsenate for five weeks. Every third day, the fish were placed in fresh test solutions. At weekly intervals for five weeks, two live fish were collected at random from each of the nine treatments. Liver, right muscle fillet, and guts (without contents) were analyzed for arsenic content. (For results of these analyses, see Table 28.)

Sorensen reported that the LT-50 (times for 50% mortality), at the same arsenic concentration, increased as temperature increased. At 60 ppm arsenic, the LT-50 at 10°C was 678 hours, at 20°C 210 hours, and at 30°C 124 hours. At 30 ppm arsenic, the LT-50 values at 20 and 30°C were 527 and 209 hours, respectively. The author concluded that arsenic uptake in liver, gut, and muscle increased with increasing temperature, arsenic concentration, and length of exposure.

Table 28 . Tissue uptake of arsenic (ug/mg wet weight)[a] by the green sunfish

Degree C and arsenic concentration in ppm	Liver Uptake Weeks				
	1st	2nd	3rd	4th	5th
10°C; 0 ppm	0.03	0.03	0.03	0.03	0.03
10°C; 30 ppm	0.03	0.06	0.12	0.12	0.21
10°C; 60 ppm	0.03	0.09	0.135	0.15	0.24
20°C; 0 ppm	0.03	0.03	0.03	0.03	0.03
20°C; 30 ppm	0.15	0.225	0.574	1.033	0.743
20°C; 60 ppm	<0.364	0.424	----[b]	----[b]	----[b]
30°C; 0 ppm	0.03	0.03	0.03	0.03	0.03
30°C; 30 ppm	<0.364	0.334	----[b]	----[b]	----[b]
30°C; 60 ppm	0.545	1.393	----[b]	----[b]	----[b]
	Gut Uptake				
10°C; 0 ppm	ND	ND	0.01	0.02	0.01
10°C; 30 ppm	0.03	0.05	0.1	0.141	0.159
10°C; 60 ppm	0.06	0.05	0.133	0.126	0.159
20°C; 0 ppm	ND	ND	0.005	0.005	0.01
20°C; 30 ppm	0.01	0.61	0.221	0.247	0.221
20°C; 60 ppm	0.65	0.226	----[b]	----[b]	----[b]
30°C; 0 ppm	ND	ND	ND	ND	ND
30°C; 30 ppm	<0.126	0.035	----[b]	----[b]	----[b]
30°C; 60 ppm	0.75	0.242	----[b]	----[b]	----[b]
	Muscle Uptake				
10°C; 30 ppm	ND	NM	NM	ND	0.029
10°C; 60 ppm	0.028	0.047	0.013	NM	0.41
20°C; 30 ppm	0.023	0.02	0.025	0.037	0.039
20°C; 60 ppm	0.017	0.015	0.015	----[b]	----[b]
30°C; 30 ppm	0.02	0.053	----[b]	----[b]	----[b]
30°C; 60 ppm	0.032	0.04	----[b]	----[b]	----[b]

[a] Values derived from author's graphs and may not be exact.

[b] No fish remained alive at these concentrations for these time periods.

ND = Not detected; NM = Not measured.

The Agency points out that, particularly for aquatic food organisms (phytoplankton, zooplankton, and invertebrates), arsenic produced the adverse effects listed by Menhinick (1962), even at sublethal concentrations. The Agency also notes the possibility of long-term adverse effects on larger aquatic organisms from sublethal arsenic concentrations. The Agency is concerned that indirect contaminations of water from use of arsenical pesticides could have long-term adverse effects on aquatic organisms through reduction in numbers of food organism and oxygen-producing algae (Lawrence 1958; Cowell 1965; Ball and Hooper 1966; and Gilderhus 1966) and through adverse effects on survival ability of larger aquatic organisms (Gilderhus 1966; Weir and Hine 1970).

(2) Population Reductions in Nontarget Mammalian Wildlife

Swiggart et al. (1972) reported on eleven dead deer (8 females, 3 males) that were found in a 600 acre area of Tennessee, which recently had been treated with an arsenical herbicide containing 39.6% arsenic acid. The product was applied aerially to agricultural land for control of Johnson grass at the rate of five gallons of mixture per acre (prepared in the ratio of 1 gallon of herbicide to 9 gallons of water). This particular use of the pesticide violated the USDA registration of the product.

Qualitative and quantitative analyses by laboratories showed a high level of arsenic in deer tissue specimens and in samples of water, soil, and vegetation from the area.

Boyce and Verme (1954) studied the effect of sodium arsenite, used as a tree debarking agent, on wildlife mortality in both commercially treated plots and controlled study areas. In several debarking test plots set up by lumber companies in Michigan, a number of deer, porcupines, and snowshoe hares were found dead. Analyses of the digestive organs indicated arsenic as the cause of death. Several controlled experiments were done on confined deer exposed to trees girdled and treated with sodium arsenite. In some studies, deer remained healthy and apparently did not lick the treated trees. In similar studies, some deer died from arsenic poisoning as shown by tissue analyses.

In a mineral preference test, two groups of adult and yearling does were exposed to trees treated with sodium, potassium, and ammonium arsenite, as well as sodium chloride. Sodium arsenite was only slightly more preferred than the other compounds, including sodium chloride. In another study, potassium arsenite was used instead of the sodium salt to determine if one form is more attractive to deer. No deer were found dead. Penned deer were exposed to sugar cubes dyed various colors to determine if the red dye added to commercial sodium arsenite formulations was attractive to deer. Deer showed only a slight preference for the red cubes.

From toxicity tests on confined deer, it was determined that only small amounts of arsenite were required to produce mortality. Death usually occurred within a relatively short time after ingestion. In one test, a yearling doe died 12 hours after ingesting a total of 4 cc of arsenite (potassium and sodium salts) in food pellets. Ingestion of foliage from treated trees caused no observable ill effects.

The animals apparently did not obtain the sodium arsenite from the girdled area of the trees but came in contact with the spillage at the base of the trees.

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[*] Copies of specific references will be provided on request. There will be a charge to cover duplication costs for such requests. A copy of the Position Document and all references are available for public inspection in the Office of Special Pesticide Reviews (WH-566), Office of Pesticide Programs, Environmental Protection Agency, East Tower, Room 447, 401 M Street S.W., Washington, D.C. 20460.

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